CASET Associates, Ltd.

10201 Lee Highway, Suite 160
Fairfax, Virginia 22030
(703) 352-0091 Fax (703) 591-2804

FOOD AND DRUG ADMINISTRATION

RADIOLOGICAL DEVICES

PANEL MEETING

(P970058)

May 11, 1998

9200 Corporate Drive
Rockville
Maryland

Proceedings By:

CASET Associates, Ltd.
10201 Lee Highway, Suite 160
Fairfax, Virginia 22030
703-352-0091

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PARTICIPANTS

VOTING MEMBERS:

NAOMI P. ALAZRAKI, MD, Chairperson. Nuclear medicine physician, Professor of Radiology and Co-Director of Nuclear Medicine at Emory University School of Medicine, Atlanta, Georgia

JUDY M. DESTOUET, MD, Diagnostic and Nuclear Medicine Physician, Chief of Mammography at Advanced Radiology, Baltimore, Maryland

MELVIN L. GRIEM, MD, Radiologist and nuclear medicine physician, Professor of Radiation Oncology, University of Chicago Hospitals, Chicago, Illinois

A. PATRICIA ROMILLY-HARPER, MD, Radiologist and Medical Director, Breast Cancer Center, Indianapolis, Indiana

JAMES B. SMATHERS, PhD, Medical physicist and Director of Medical Physics, Radiation Oncology, UCLA School of Medicine, Los Angeles, California

TEMPORARY VOTING MEMBERS:

BRIAN S. GARRA, MD, Professor and Vice Chairman of Radiology, University of Vermont, Burlington, Vermont

ARNOLD W. MALCOLM, MD, Radiation Therapist, Medical Director, Provident St. Joseph Medical Center, Burbank, California

NON-VOTING MEMBERS:

PATRICIA WHELAN, MS, Social Worker in the AIDS Center, St. Vincent Hospital, New York, New York.

P R O C E E D I N G S (9:08 a.m.)

Agenda Item: Call to Order and Chair's Introduction.

DR. ALAZRAKI: My name is Naomi Alazraki. I will be chairing this meeting. I would like to call this meeting of the radiological devices panel to order.

I would also like to request that everyone in attendance at this meeting sign in on the attendance sheets which are available at the door.

I note that the voting members present constitute a quorum, as required by 21-CFR, Part 14.

At this time, I would like each of the panel members to introduce him or herself and state his or her specialty, position title, institution and status on the panel . I will start with myself.

I am Naomi Alazraki. I am a specialist in nuclear medicine, professor of radiology at Emery University School of Medicine, co–director of the division of nuclear medicine, and chief of nuclear medicine at the VA Medical Center in Atlanta.

I am a member of the panel and am now chairing the meeting.

DR. ROMILLY-HARPER: Dr. Pat Romilly-Harper. I am a diagnostic radiologist, sub-specializing in breast cancer detector, director of the Indianapolis Breast Center, and a

voting member of the panel.

DR. DESTOUET: I am Judy Destouet, chief of mammography for Advanced Radiology in Baltimore, Maryland. I am a voting member of the panel.

DR. YIN: Lilian Yin. I am the division director, Center for Devices and Radiological Health, FDA.

MS. WHALEN: My name is Patricia Whalen. I am a clinical social worker at St. Vincent's Hospital in New York City. I am the consumer representative to the panel, and a non-voting member.

DR. GRIEM: I am Dr. Melvin L. Griem, emeritus professor, University of Chicago, a radiologist who currently runs an imaging lab at the university.

DR. SMATHERS: Dr. Jim Smathers, a medical physicist, department of radiation oncology, UCLA.

DR. GARRA: Brian Garra. I am vice chairman of radiology and professor of radiology at the University of Vermont, and a voting member of the panel.

MR. DOYLE: My name is Bob Doyle. I am a reviewer in the radiological devices branch and executive secretary of this panel. I am not a voting member.

DR. ALAZRAKI: Dr. Arnold Malcolm is not in his seat, but when he comes, we will have him introduce himself as well. In the meantime, Mr. Doyle, would you like to make some introductory remarks?

MR. DOYLE: Yes, I would. Thank you. I would like to read a statement concerning appointments to temporary voting status granted on April 22, 1998, by Dr. Bruce Burlington, director of the Center for Devices and Radiological Health.

Pursuant to the authority granted under the medical devices advisory committee charter dated October 27, 1990 and as amended April 20, 1995, Dr. Brian S. Garra and Dr. Arnold W. Malcolm have been appointed as voting members of the radiological devices panel for the May 11, 1998 panel meeting.

For the record, these individuals are special government employees and consultants to this panel under the Medical Devices Advisory Committee.

They have undergone customary conflict of interest review. They have reviewed the material to be considered at this meeting.

Now I would like to read the conflict of interest statement for this panel meeting. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of any improprietary.

To determine if any conflict existed, the agency reviewed the submitted agenda and all the financial interests reported by the committee participants.

The conflict of interest statuses prohibit special government employees from participation in matters that could affect their, or their employers, financial interests.

However, the agency has determined that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interests of the government.

The agency has determined that all participants may participate fully in the discussion before this panel.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record.

With respect to other participants, we ask in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

If anyone has anything to discuss concerning these matters, please advise me now, and we can leave the room to discuss them.

Seeing no one, I will proceed.

FDA seeks communication with industry and the

clinical community in a number of different ways. First, FDA welcomes and encourages pre-meetings with sponsors prior to all IDE and PMA submissions.

This affords the sponsor an opportunity to discuss issues that could impact the review process.

Second, the FDA communicates through the use of guidance documents. Toward this end, the FDA develops two types of guidance documents for manufacturers to follow when submitting a premarket application.

One type is simply a summary of the information that has historically been requested on devices that are well understood, in order to determine substantial equivalence.

The second type of guidance document is one that develops as we learn about new technology.

FDA welcomes and encourages the panel and industry to provide comments concerning our guidance documents.

Finally, I would like to remind you that the meeting of the radiological devices panel tentatively scheduled for the remainder of the year will be held August 17 and 18, and November 16. Please mark these dates on your calendar.

You may wish to pencil these dates in, and please recognize that these dates are tentative at this time.

I would now like to introduce Dr. Robert Phillips,

the chief of the radiological devices branch, who will give the panel a brief report on the follow-up actions that have resulted from recent panel meetings.

DR. PHILLIPS: I just have one item for you. By the way, good morning. Thank you for coming.

On March 12, we approved the hallogic bonsinometer submission. If you recall, you discussed that and made recommendations to us.

We will have copies of the summary of safety and effectiveness either available for you this afternoon, or we will mail them out to you some time this week.

DR. ALAZRAKI: I would like to go back and ask Dr. Arnold Malcolm to introduce himself, since he wasn't here when the rest of the panel did introductions, by your specialty and institution affiliation.

DR. MALCOLM: My name is Dr. Arnold Malcolm. I am medical director of radiation oncology, Provident St. Joseph's Medical Center in Burbank, California.

DR. ALAZRAKI: Thank you, and thank you, Dr. Phillips, for your remarks.

We will now proceed with the two of the first half-hour open public sessions of this meeting. The second half hour open public hearing session occurs following the panel discussion and before the panel recommendation and vote.

Agenda Item: Public Comment.

At these times, public attendees are given an opportunity to address the panel, to present data or views relevant to the panel's activities.

If there are any individuals wishing to address the panel, please raise your hands and identify yourselves now.

Okay, seeing none, we will continue. I would like to remind public observers at this meeting that, while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the chair.

Agenda Item: OPEN COMMITTEE DISCUSSION. Charge to the Panel.

I would like to at this time request that persons addressing the panel come forward to the microphone and speak clearly, as the transcriptionist is dependent upon this means of providing an accurate transcription of the meeting.

If you have a hard copy of your talk available, please provide it to the executive secretary for use by the transcriptionist, to help to provide an accurate record of the proceedings.

We are also requesting that all persons making statements, either during the open public hearings or the

open committee discussion portions of the meeting, disclose whether they have financial interests in any medical device company before making a presentation to the panel.

In addition to stating your name and affiliation, please state the nature of your financial interest in the company. Of course, no statement is necessary from the employees of that company.

Definition of financial interests in the sponsor company may include compensation for time and services of clinical investigators, their assistants and staff in conducting the study, and in appearing at the panel meeting on behalf of the applicant, or direct stake in the product under review -- for example, inventor of the product, patent holder, owner of shares of stocks, et cetera -- or owner or part owner of a company.

We can now begin the first open public portion of this meeting. We will now proceed with consideration of the PMA.

We will begin with the presenters from R2 Technology, Incorporated. They will be talking about PMA application O970058, for their M1000 ImageChecker device, a computer-aided detection system for screening mammograms.

We request that the presenters for R2 Technology, the sponsor of this premarket approval application, sit at the presenters table.

After you have finished all your presentations, we ask that you turn the presenter's table over to the FDA speakers, who will follow.

I would like to introduce Dr. Alan Stein, vice president for regulatory affairs, who will begin the company's presentation of the information contained in the PMA we are considering today. Dr. Stein?

Agenda Item: OPEN COMMITTEE DISCUSSION. R2 Technology, Inc. Presentation of P970058.

DR. STEIN: Dr. Castellino will actually do the introduction for the company.

DR. CASTELLINO: Good morning, ladies and gentlemen of the panel, and ladies and gentlemen in the audience.

It is my pleasure on behalf of the company to indicate our thanks to the panel for listening to our presentation, as we go through the clinical trials that hopefully will prove the efficacy of this device.

My name is Ronald Castellino. I current serve as medical director for R2 Technology. I have been in that position for approximately seven months.

My day job, so to speak, is as chairman of the department of radiology at Memorial Sloane-Kettering Cancer Center. I have had that position for the past eight years.

Prior to that time, I was at Stanford Medical

School in California for approximately 25 years.

After my few introductory comments, I would like to go through the schedule for the presentations. I will talk for approximately 10 minutes, talking about the overview of the technology, how it is used in clinical practice, and some of the reasons why we think this technology is important in the care of patients who potentially have breast cancer.

I will be followed by Dr. Kass, who will also talk for about 10 minutes, who is in charge of the radiology program.

She is a radiologist at Kaiser Permanente in Redwood City, California. Dr. Kass has been a user and PI on some of the clinical trials you will hear discussed this morning.

Importantly, she has continued to use this system as an investigational device in her clinical practice on a day-to-day basis.

Following Dr. Kass, Dr. Stein will talk for approximately 30 minutes. He is the vice president for regulatory affairs for the R2 Technology company.

He has been in charge and has overseen the extensive clinical trials that he will report to you about, trials that relate to the efficacy of this product and, importantly, in some part have been co-designed with input

from the FDA, to ensure that we have met some of the requirements that you would like to see us do.

Below the line, on the bottom half of the screen, are five other individuals who are available for comment or questioning.

The three on the left, Dr. Brem, Vjorny and Cederbom are physicians, all who have active practices in breast imaging.

Dr. Brem is full time in breast imaging at Johns Hopkins University and was involved in some of the early clinical trials with this unit.

Dr. Cederbom is a PI on the more recent clinical trials. He is at the Ochsner Clinic in New Orleans.

Dr. Vjorny is an associate professor of radiology at the University of Chicago. Dr. Vjorny has had a long-standing interest in the computer analysis of images, has contributed some important and seminal articles to the literature in this regard, and has been a very valued consultant to the company.

In addition, Dr. O'Shaughnessey, who is the director of technical marketing for R2 Technology has been in charge of the clinical trials and the data manager. She is here available also for questioning. Mr. Kennedy is a consulting statistician to the company, who has helped design the statistical aspects of the study and can respond

to some of the statistical questions if necessary.

I would like to indicate at the outset that the company indicates that the utilization of this technology has been specifically addressing the issues of screening mammography.

At this time, there is no attempt to claim any use in the more diagnostic aspects of mammography.

Now there are multiple challenges that I think we all know about in the screening mammography program. I would like to indicate at the outset, however, that the screening program has been extremely successful in a demonstrated decrease in mortality in women with breast cancer.

This is particularly true, perhaps, in the last 10 years when industry has brought together some important improvements in technology, when the radiology community, along with the American College of Radiology and the Federal Government, in fact, have insisted upon a review process leading to certification of radiologic imaging sites that do radiology as well as radiologists.

All of this has, I think, ended up in a situation where mammography, which is an excellent tool at early cancer detection, has been used quite effectively.

However, there are problems. The problems relate to, as we see on the slide on the right, the attempt to try

to tease out findings on a radiologic image, very subtle, often superimposed upon a very complex background of normal breast tissue that may represent the earliest signs of breast cancer. In fact, radiologists often do a good job in this very difficult task.

However, in screening, in addition to the complex interpretations that radiologists are faced with, they are also faced with the fact that often there is a high volume of cases, the viewing time for each case can be short and the incidence of cancer in the screening population is extremely low.

Perhaps one in every 200 screening mammograms will eventually turn out to have a diagnosis of biopsy proven cancer.

This means that, in fact, that although the tool of mammography is extremely good at detecting early cancers, the limitations of any human observer, no matter how experienced, will suggest that at times there are cases that will be read as negative when, in fact, there is evidence of cancer on that image.

Not surprisingly, the breast imaging community has very correctly looked at this problem. We have shown here a sampling of cases from the literature of individuals, of reports where, knowing that a cancer was diagnosed on a current study, these investigators have looked back at a

prior mammogram to try to determine if, in fact, there was evidence of a cancer being there.

These can be defined as either interval cancers, as you can see in the top five articles, or screen-detected cancers.

Now, the methodologies of some of these types of reviews have been quite different. Sometimes the radiologist has looked at the current and compared it to the prior study, knowing where to look. At other times it has been a blinded review of one or more radiologists in a panel.

No matter how it is done, you can see that in anywhere from 30 to 60 percent of cases, in retrospect there are findings on the prior mammogram that were overlooked that, in fact, could be viewed as the earliest sign of cancer.

Now, to approach this problem, it has been suggested -- and some places do this and certainly some Europeans have adopted this quite strongly, that if you added a second reader to the process, you would be able to decrease, in a sense, the amount of false negative studies that a radiologist would have.

This is a study from Sweden, from Upsilon, Sweden, looking at 72 cases of cancer, biopsy proven, that were detected by one or two readers.

You can see that radiologist number one and number two both detected 56 cancers which led to a biopsy proven diagnosis of cancer.

Radiologist one found 14 cancers that radiologist two did not find and radiologist two found six that radiologist one did not find.

You can see the added value, very clearly, of a second reader, ranging anywhere from either eight to 18 percent in this study.

It is probably for this reason that we feel -- and the imaging, the medical physics imaging community -- has looked at using computers as an aid to detection of these lesions.

I would like to emphasize that we are talking about CAD, an acronym, that we use to represent computer aided or assisted detection.

This is not a diagnostic device. The diagnosis is really in the hands of the radiologist. This is a device that will help the radiologist not overlook a finding on a radiograph that they might do the in the course of a busy clinical day, and have the radiologist go back and be able to reassess that specific lesion and make a diagnostic decision as to what to do with the patient.

It is a perceptual aid and, of course, as a computer, it is never tired.

There are two major codes that have been used by this company to evaluate these images. The first is pretty straightforward, I believe. It is a microcalcification code.

The system will search the image for clusters of what might be called bright spots which are suggestive of microcalcification.

Having identified these -- and it depends upon numbers and size and distance from each other, all present in the handbook that you have gotten -- it will indicate the presence of these clusters of bright spots by a triangle, and the triangle will be placed in the geographic center or centroid of these clusters.

The second code has been termed the mass code and requires a bit of explanation. The system, in fact, does not specifically search for masses, as a radiologist might define a mass.

In fact, it searches for patterns of dense regions within the breast parenchyma associated with radiated lines.

Now, these patterns that the computer searches for would be called masses by radiologists or, in fact, architectural distortions.

Schematically, we have tried to demonstrate the range of types of densities or masses one might encounter on a mammogram with the increasing likelihood that this might

be marked by the ImageChecker system.

It is important to point out that the mass codes, so-called mass code, will in fact detect architectural distortions, because the density that these distortions present and by the irregular characteristics of the edge margins at times.

It is also important to note that the mass code cannot identify the lesions that the mammographer will call emerging densities.

There is no temporal comparison between the current studies and the prior studies currently. So, the emerging aspect of emerging densities, this code cannot detect.

This code can detect a mass that is present. It just cannot indicate if it is emerging or not. So, there is some success at identifying emerging masses, because they are masses, and architectural distortions.

I would like to urge all of you, when you hear about the mass code, we are not simply talking about the mammographic mass lesions, but also about other subtle alterations in the breast.

Now, how is the system used? It is pretty straightforward once again. The mammograms are performed by the technologist and QAd by the technologist in the standard fashion.

Prior to mounting the mammograms on the motorized viewer, which is the usual way this happens, these mammograms are put into the ImageChecker system.

The individual mammograms -- these are standard images, the standard four views for screening -- two from each breast -- are digitized to the 50 micron level. Far in that process, the mammograms are removed and placed on the alternator.

During this period of time, during the digitization of the images, the computer code addresses these digitized images looking for microcalcifications and masses.

When the radiologist sits down to review the studies -- as we see here in this close-up view of this motorized viewer -- the radiologist first looks at the images in the standard fashion. These are the film images as they usually do in clinical practice.

Observations are made. Decisions are made upon actionability. At that time, a button is pushed in the center of the console and the similar images that are now the digitized images from the ImageChecker are portrayed on these monitors with signals, triangles or asterisks, indicating to the radiologist areas on the mammogram that need to be reviewed.

They are not reviewed on these small monitors. In

fact, these monitors are designed not to represent diagnostic images, but in fact, they are designed to be triggers for the radiologist to move from this monitor back to the original image, to make a reevaluation of that area and a reinterpretation if necessary.

This is what an image might look like after the ImageChecker has done its work. A triangle is placed in an area where there are small bright spots indicative or suggestive of microcalcifications and an asterisk is placed in an area that is indicative or suggestive of a mass or other type of distortion.

The numbers of markers on a film are important considerations. In the early version of the product, I am told, there are multiple marks on every image, multiple marks of calcification and of masses. This could be very distracting, obviously, to the radiologist.

The computer code that is used as a basis for all of this work was licensed from the University of Chicago, from Dr. Doye's exceptional laboratory there. R2 Technology has put in place a very important and very large development team that substantially enhances code.

Currently, as you will see in the cases presented by Dr. Stein, the average number of marks per film on cases that are normal is approximately one, and of course, the average number of marks on films where a cancer is

eventually proven to be present by biopsy proof is approximately two.

Per case, then, four images per case, four films per case, approximately four marks per case, one on every film.

I would like to turn the next part of the presentation over to Dr. Kass. As I have mentioned before, she has been a principal investigator on some of the clinical trials and she is an ongoing user as an investigational device in her practice in Redwood City.

DR. KASS: Thank you, Dr. Castellino. My department at Kaiser Redwood City in the San Francisco peninsula, is one of the test sites, the clinical test sites.

We are a very busy department. In addition to doing community radiology, it is a neurological referral center. We have got a lot of stuff going on in addition to mammography.

We have six NQSA certified radiologists. We do a total of approximately 10,000 to 11,000 mammograms per year.

We have been using the ImageChecker in our screening mammograms for over a year now. Separately, I have been involved in some of the retrospective studies at the R2 facility as a paid consultant, one of the designated readers that Dr. Stein will be discussing in the next talk.

I do not have any financial equity interest in the company, but they did pay my way here.

I would like to tell you a little bit about how we actually use the ImageChecker in my department and also show you a few cases from some of the retrospective studies that may clarify a little bit of what we are talking about here.

You can look at the process of reading a mammogram as involving two basic tasks, perception and interpretation.

In this slide the radiologist is using two tools to maximize her performance in the perception phase of her reading.

She has got a magnifying glass to help her pick up fine detail on the mammograms, but she also has a computer, the R2 ImageChecker, to help her pick up subtle alterations in pattern on the mammogram.

I am going to show you four cases, to help familiarize you with some of the terminology and concepts that Dr. Stein will be covering in detail in his discussion of the data.

This is what we refer to as a current mammogram from a retrospective study that compares current cases that are biopsy proven cancers with prior mammograms, mammograms that we have found in the record from the previous years that we now know, from this year's studies, have breast cancer.

So, this is one of what we call currents. What you are seeing on a screen is actually a composite of the actual mammogram film and the mark that, in reality, would be appearing on the small digitized image of the mammogram showing up on the mini-monitor.

There are four little monitors, each corresponding to one of the four views of the screening mammogram on the panel.

The way I use the ImageChecker, the ImageChecker does not in any way affect the traditional way of reading the mammogram. It is an additional perceptual aid. It gives me a perceptual edge, similar to the magnifying glass, only fancier.

I look at the mammogram as I normally would through the entire reading, look at it with a magnifying glass to make sure that I am not missing features that are so small that they would not be readily apparent to just looking at it with my slightly less-than-perfect vision.

I use the magnifying glass. Everything is traditional. Then, before I go on to finalize the dictation that I have already got in my mind, I hit the white button on the console. At that point, not before, the ImageChecker digitized pictures become visible.

I then look at those pictures, see if there are any marks on them, any mass mark asterisks or any

calcification mark triangles.

I go back, look at those areas on the mammogram to be sure that I have made all the relevant observations in that area.

The unit is really very easy to use. It is almost intuitively obvious. Also, for a radiologist that reads a lot of mammogram it becomes really, in almost all cases, very easy to say, that is summation, those are skin calcifications.

Again, the mammogram doesn't say this is a cancer, take it out. It says -- the ImageChecker says -- these are features that the algorithm in the artificial intelligence says can be part of the pattern of early breast cancer.

What it is saying is, look here, and you make your judgement of what does this mean. It has nothing at all to do with altering my judgement or affecting my judgement. It is a perceptual aid. It gives me an edge.

So, on this mammogram we are seeing the regular films as they would be hung in their usual form on the mammoviewer board.

This slide also shows this asterisk which would, in the real world situation, appear as the digitized images come up on the bottom of the screen.

If I had not noticed this rather large breast cancer here, I would have looked down at the screen and

said, wait a moment, there is a mass mark there. Did I really look at this area or was I thinking about a neural angiogram I did at 2:00 a.m. the night before.

I would go back and look at that area and I would perceive that there is a mass here. In this case -- again, this is one of our currents from the currents and prior pairs of the retrospective study -- this case was found.

The radiologist perceived the abnormality. In the radiologist's judgement this was an actionable lesion. The case went to biopsy and an invasive ductal carcinoma was found.

Subsequently, we took this case, age 53, ran it through the ImageChecker and, big surprise, the ImageChecker puts a mass mark on this rather obvious mass.

You say so what. That wasn't her first mammogram. She had been in a screening program, a screening with NQSA certified radiologists, experienced people.

The year before she had had this mammogram. Retrospectively, running it through the ImageChecker, the lesion is marked. This is just a digitally magnified picture that we derived from the mammogram. It was not a spot mag that was done back at that time. This is just something that we have done to make it slightly more visible in this projection.

There is a lesion there. It is on the spectrum of

round to stellate, and the ImageChecker detects the features of a mass here.

This unfortunately does not project well. It is the calcification code. These triangles marked calcifications.

We know from this biopsy proven screening mammogram, that is a cancer in there. Ran the current, the ImageChecker puts a calc mark on it. Ran the prior -- I think it is a 15 months before in this case -- and that cluster of microcalcifications is marked here.

You can see there are additional marks. Skin calcifications, vascular calcifications, it is usually very simple to say, this is not actionable. This is typical skin calcifications.

This is the final slide I am going to show. It is another example of ImageChecker picking up the features of a mass. Again, it does not say this is a cancer. It says, this area meets the algorithm. Look here. This is an area where your judgement is needed.

Age 60, was not picked up by the NQSA certified radiologist. It is, however, marked in retrospect by the ImageChecker, the mass.

I want to emphasize again, it is not just completely classical star-shaped stellate masses out of a textbook that it picks up.

It will pick up these little irregular things. It is a spectrum. They are more likely to be picked up when

they are stellate. It also can pick up the features of many lesions that fit in the category of what we think of as masses.

Okay, in my department, using this for a year, we like it. We use it. I find it does not slow me down. It was easy to learn. I have become very happy using it.

Again, it is possible to read a mammogram without a magnifying glass, but I prefer to have the magnifying glass there.

Over the past year, I have come to the point where I prefer to have the ImageChecker there. It gives me a perceptual advantage.

It doesn't affect traditional reading of the mammogram. It is a tool, another tool, to decrease the risk of observational lapses.

We found it to be very sensitive in picking up subtle features that may indicate the presence of early breast cancer, and I think it has been of benefit to our patients.

Okay, Dr. Stein will be presenting data on a very large number of cases from the studies and is going to go into some details here.

DR. STEIN: Thank you, Dr. Kass. At this point I will be reviewing the rather extensive clinical trials that are in support of the claims for the device for the

indications listed on the right.

The ImageChecker system is a computer-aided detection system with image analysis and visual display capabilities that is intended for use as a perceptual aid for radiologists reading routine screening mammograms.

Further, this system is designed to identify and mark regions of interest that have been identified by the company's proprietary signal processing algorithms, in order to bring those regions of interest to the attention of the radiologist after they have completed their usual interpretation of the mammogram.

As such, the system assists the radiologist in minimizing observational lapses by identifying those areas on the original mammogram that may warrant a second review.

Starting in November of 1996, the company had a number of meetings and a large amount of correspondence with FDA staff in order to identify the clinical issues and protocols which would be considered necessary to define the safety and efficacy of the device.

They really devolved down to these three major study areas. The first was a prospective study to determine whether the use of this system would somehow increase the diagnostic work-up rate. This was the first question of concern.

The second question was to determine what was the

total number of cancers that are missed during the current screening mammography process and what the ImageChecker system's ability would be to mark those missed cancers.

Finally, a precision study to clarify the sensitivity of the system to marking lesions on a large consecutive screening mammography pool of biopsy proven cancer. Finally, an intrasystem performance reliability test.

I am going to go through these slowly and bit by bit. Again, the purpose of the first study was to determine whether the use of the ImageChecker system would increase the number of patient work ups in a prospective multi-center clinical trial.

In other words, is it possible that the marks on the ImageChecker would somehow unduly influence the radiologist and cause them to increase their work-up rate inappropriately.

To this end, we designed the study as follows. First, of course, we recruited the sites and radiologists, all of which were NQSA certified.

The participating radiologist requirement was simply that they read 100 routine screening cases a month.

The baseline data was taken from hospital statistics and records, describing the number of screening mammograms and work-up rate on a month-by-month basis by the

site and the radiologist involved, and there was a minimum four-month period involved.

On this basis, we then installed the system at the hospitals and the medical and technical staff were trained in the operation of the ImageChecker system, and any work flow changes were established.

Now, as you can imagine, for the radiologists, given Dr. Kass' comments, the training is actually very simple. It is really how to hit a button and really anticipate what the device can mark.

For the technologist, as Dr. Castellino described, there is the method, this extra step after the films are processed, of putting them through the digitizer, so that they can then be analyzed by the ImageChecker unit.

This is the only additional step prior to them hanging the films for the radiologists to do their standard review.

All asymptomatic screening mammography cases were processed on the system, and every month we collected the number of screening mammograms and work-up rate both for the site and the radiologist and performed any reconciliations for cases that were, for one reason or another, not included.

Then at the end of the study which ran, again, for a minimum of four months at each side, we computed 99

percent Clausen-Pearson(?) statistics, and also the chi squared test.

Now, the data were reported on 14 radiologists from five institutions. Two were Kaiser, representing managed care, and three were from the Oschner, Susan Coleman and Vanderbilt, which were dedicated breast clinics with university affiliations, of course.

You can see on the slide at the right that the baseline number of cases was almost 24,000 cases, and the average work-up rate across those 14 radiologists was 8.3 percent.

In the post-installation interval, we collected nearly 15,000 cases. The average work-up rate of those radiologists was 7.6 percent. The observed 7 percent decrease in work-up rate was not statistically significant.

In fact, we conclude that in a prospective multi-center, multi-radiologist trial, comparing work-up rates before and after installation of the system, that there was no statistically significant difference in work-up rate for the group overall or for any individual radiologist.

The purpose of this study, now, was to determine the capability of the system to correctly identify microcalcifications and masses in screening mammograms that were acquired in the nine to 24-month interval prior to the screening detected cancer, particularly those cancers that

were determined by radiologists.

That is, in other words, we conducted a very, very large study to determine how visible breast cancer was in retrospect and how well the system could mark those cases.

Now, the methods for this were really quite involved, and I will need about a half dozen slides to go through this, but I think it will make the conclusions a lot clearer.

Collection of case material. Once again, all sites and radiologists who participated in the study -- whether they were site radiologists, panel radiologists or designated radiologists -- were all NQSA certified.

We collected all consecutive biopsy proven cancers detected from asymptomatic screening mammography in a two or three year interval from each of the participating sites in the period from 1994 to 1996.

For the purposes of this discussion, we use the term currents and priors very regularly. Currents we defined as screening films in which the cancer was detected that was subsequently confirmed by biopsies.

Priors are the most recent screening films in the interval nine to 24 month earlier.

Normals, as opposed to just a normal, were defined formally as routine screening mammograms that were read as normal and confirmed by at least one other follow up exam

that was also read as normal, so that we were sure that there was no possibility of a lapse or anything emergent in that early case.

To prepare the case material, we went out to each of the participating sites, and the site radiologist reviewed the actual case and developed a gold standard for the current case; that is, they created an overlay.

They defined on the overlay the position of the biopsy proven lesion or lesions, and classified the lesions in terms of their being microcalcifications or masses.

That information was then provided to another NQSA certified, what we called designated radiologist, who took the current overlay and all relevant patient information from that current cancer and compared that to the prior film for that patient.

The goal of the designated radiologist was actually to try to develop a gold standard for the priors and we didn't want the site radiologist to do that because there was, of course, the possibility of some bias.

The designated radiologist looked at those cases. If there was nothing visible in the image, that is, if the feature was invisible, that was separated into one set, and the invisible priors were excluded from review, except for 20 cases which we did use for quality control purposes.

If the lesion was visible, the designated

radiologist created an overlay, a gold standard for that prior, which we used for subsequent analysis and comparison.

We also, as a matter of point, reviewed those cases that were either unilateral, had previous breast surgery, and conservatively excluded them from review.

As I will discuss a bit later, the panel radiologists were given a very minimum of information, and these patients with prior surgery would have had to have much more extensive documentation.

As such, since they were a relatively small proportion of the cases that we used, we decided to conservatively exclude them, although we did include their numbers in the denominator. I will review that again further, later.

Now, we had to now prepare these case sets. A case set, there was a nominal goal of having 70 to 75 visible priors mixed with five quality controlled invisible priors, and 20 normals and 20 currents that would be reviewed by every participating panel radiologist.

These 20 currents and 20 normals that were reviewed by all radiologists, provided us with an opportunity to assess the radiologist's performance in the test situation, and to see, under the test situation, if they were performing acceptably, and then to provide ourselves a mechanism for making an inter-radiologist

comparison for the purposes of justification of pooling.

Now, since these cases were the original films, and these records need to be made available at any moment to the hospital, as soon as we anticipated getting on the order of 70 to 75 cases, we would start to schedule the panel radiologists.

Whatever number of visible priors were available on the date of the first panel radiologist of the case set, that is how many visible priors were used for the rest of that case set, and that is why there is a bit of variation here.

You can see that as a result, we reviewed a total 286 visible priors in the study.

Now, the panel themselves, as noted again, all panel radiologists were NQSA certified. They reviewed the cases independently.

There were no one or two radiologists together, just one at a time looking at that series.

If this is not clear, they had no access to ImageChecker results. This is just a retrospective review of the data. This is not directly related to any performance issues of the ImageChecker. This was to establish what type of cancers are missed, or potentially missed, in the prior films.

Now, the instructions for the reviewers were as

follows. They were told there was a mixture of positive and negative cases and, of course, not the prevalence of each type.

They were given only patient age and information about film markers, BBs and such, and they were asked to operate at their usual clinical threshold and to provide the location of the primary or secondary or the first or second most suspicious areas, to circle those if they saw any on the overlay, to tell us the characteristics of those lesions -- that is, those suspicious areas, in terms of them being masses or microcalcifications -- and to give us an assessment recommendation using the Byrette's(?) categorization.

The ImageChecker was also, in parallel, run on all the visible priors. Visible priors were run through the ImageChecker system.

The print-outs of the ImageChecker system were then reviewed by the designated radiologist who created the gold standard for the prior, and they scored whether the system had correctly or incorrectly marked the case.

The scoring was actually parallel for both. For the doctors on the panel, we created what we called a consensus and actionability.

That is, for every case, how many radiologists on that panel identified the location of the lesion correctly

on at least one view, and correctly classified the identified lesion and finally, had categorized that as an actionable case -- A,S or M on Byrette's.

The ImageChecker was scored to be correct by the designated radiologist if, just as the panel radiologist, they identified the location of the lesion correctly on one view and correctly classified the identified lesion. Then appropriate statistical analyses were performed.

The results of this study were collected from cases from 13 institutions. These institutions represent private clinics, managed care, university hospitals, dedicated breast centers, a full spectrum of where mammography occurs in America today.

The results are as follows. In terms of data accountability, there were, out of all these hospitals, 2,551 cancer cases listed.

Of those, there were 1,468 excluded, the majority because they were symptomatic, and the purpose of the study was to review the benefits of the device for asymptomatic mammography.

Four hundred and thirty cases of these were not available. The other major reason for the exclusion was that the lesion itself was not evident mammographically.

The other smaller categories that represent three to four percent are mostly clerical issues and are described

in detail in the PMA submission.

That left us with 1,083 asymptomatic current cases from a consecutive population. Given the incidence that Dr. Castellino had listed in his prior slide, this would result from a pool on the order of a quarter million asymptomatic screening mammograms.

So, this makes it, I am sure, the largest study that has been published of this type.

Of the priors, there were 493 priors that were acquired in the nine to 24-month interval prior and that were available. There were no other criteria.

Now, of those 493 priors, they were broken out this way by the designated radiologist. There were 286 cases that were visible, and therefore were reviewed by the panel radiologists.

There were 141 cases that were invisible, of which we pulled 20 for quality control, as we just described. There were 62 who had prior surgery, which were not included for review by the panel radiologists, although they were included in the overall denominator of the study.

There were four that were not available. That is, at the time of the fourth case set, there were still some queries pending on these four cases. Therefore, they could not be included in that final case set review.

The results. First of all, we have to look at the

results of those panel radiologists based on the 20 currents and 20 normals that they read.

Based on our input from our advisory committee, we had made one particular criteria of performance for these radiologists using the currents and normals, and that was that a case would be excluded if any radiologist was performing less than 10 out of 20 in terms of sensitivity or specificity.

It was felt that that radiologist would have been somehow very significantly affected by the test environment. Therefore, in the event that that happened, their case was excluded, and another radiologist was immediately brought in to substitute for that radiologist, assuming they performed at least 10 out of 20 or better in sensitivity and specificity.

Therefore, the range of sensitivity across the four case sets ranged from 79 to 87 percent, with an average sensitivity of 83 percent on these cases. The specificity was 81 percent, ranging from 76 to 88 percent.

As noted on the bottom of this slide, you can see there were three exclusions, one for a radiologist who performed in the test situation with only eight out of 20 on those known cancer cases.

In the second case set there were two exclusions, one for a radiologist whose sensitivity was seven out of

nineteen and the other nine out of 20.

The reason there were 19, just to allay any questions was, we couldn't read one of the responses on their data form. However, since they were so far below 10 out of 20, we didn't even both to clarify what the difference was.

Now we come to the actual meat of the results. The consensus study demonstrated the following. Of those 286 cases, they range from, of course, zero out of five to five out of five.

What you should read from this is that these cases in this area here have very, very subtle features. Maybe in some sense they are not very specific, given the fact that zero out of five radiologists would call anything on those cases.

As we go to higher and higher consensus, the characteristics of these lesions are not only very visible, but they are also very actionable.

In fact, similarly, the ImageChecker's ability to identify these areas was actually rather extraordinary. Even in cases where no radiologist considered them visible and actionable, the machine was able to mark a third of them.

In fact, cases where only one out of five radiologists was able to identify the area, the machine

marked those areas 53 percent of the time.

By the time we are looking at consensus associated with a super majority of doctors -- four out of five and five out of five -- the machine's overall performance is actually a total of 83 percent, between 79 and 92.

Looking at it another way, if we looked at the majority consensus -- that is, a simply majority of three out of five, four out of five and five out of five doctors, there were 112 out of 493 prior cases, or 22.7 percent of cases, that were considered visible and actionable by these independent blinded radiologists.

The machine was able to identify the correct feature 81.3 percent of the time, and this is for all cancers. I mean, these are all the calcifications and all the masses. There was no segmentation of these materials that were provided to those radiologists.

If we look at it at a higher level, at a super majority, 15 percent of those cases, 74 over 493 cases, were considered obvious and actionable by a super majority of radiologists, and the machine marked 85 percent of those.

If we go all the way up to full consensus -- that is, 100 percent of the radiologists who saw those cases, saw them and considered them obvious and actionable -- there were 7.3 percent of the cases, and the machine marked 92 percent.

We looked at this as a function, of course, of the two major codes that are involved in the algorithms, the microcalcification code and the mass code.

You will notice that based on either a majority, super majority or 100 percent cut off, the calcification code is extraordinary. It marks 95 percent of the cases to 100 percent of the cases. It is very, very, very sensitive identifying calcification features.

For masses, which for our definition is everything that is not a calcification, the system was able to mark between 74 percent of those that were visible by a majority of doctors, to 87 percent by those that were visible and considered actionable by all doctors.

We conclude from this study that the ImageChecker system can correctly mark a high percentage of all those prior cases that were judged actionable by a majority of radiologists.

In fact, it should be appreciated again that those priors were acquired in the prior nine to 24-month interval before the cancer was actually detected on a subsequent routine screening study.

Again, the ImageChecker does mark a very high percentage of cases considered visible and actionable in retrospect, by an independent panel of NQSA radiologists, and those cases were acquired nine to 24 months before the

cancer was detected providing, as Dr. Kass said, an opportunity to steal more time from cancer.

The third leg of the study were the precision studies. The precision studies were to determine the sensitivity of the system in marking lesions on the screening mammograms that had biopsy-proven cancer; that is, the 1,083 current cases that were just described in study two, as the basis on which we pulled the priors.

Again, this was a large consecutive series of screen-detected cancers. The methods were as follows. You saw them largely yourself.

The currents were reviewed and a gold standard was established by the site radiologist. All of those currents were run on the ImageChecker system.

The print outs were brought back to the site radiologist who created the gold standard overlay and scored by the site radiologist, in a manner directly analogous to the way the designated reader radiologist reviewed the priors.

In this manner, again, we kept the company arm's length for any sort of review and analysis and implication of bias.

As noted before, these were all consecutive cases of asymptomatic screening mammography. The site radiologist, as we said before, created the gold standard.

The system was scored by the doctors at the site and not by the company, and statistical analysis performed as appropriate.

Participating institutions were the same as we just discussed, and again, this is just for being consistent. This is the data accountability table we previously described to you.

The results, for those 1,083 cases, 404 were microcalcifications. The machine marked 98 percent of those correctly.

Of the masses, all masses, all 679 other cases that were not calcifications, the machine marked 74.7 percent of those correctly.

As Dr. Castellino had noted, in terms of the number of marks per case for all cancer, the average number was 7.22 marks per film case, or 1.8 marks per film.

Of the normals, of which we had collected 100 to evaluate this particular characteristic of the device, the average number of marks per film was 3.6 or .9 per film.

We conclude from the sensitivity study that the system can correctly mark a very, very high percentage of lesions from a large, consecutive and representative sample of cancers identified during standard screening mammography of asymptomatic women.

The final aspect of the precision studies was to

determine the intra and intersystem reliability of ImageChecker in identifying and marking those regions of interest associated with cancer.

This reliability study was based on the selection of 25 well-characterized cases from the currents where the cancer was visible with both the CC and the MLOU.

There were 14 microcalcs and 11 masses that were used. We took only the two views from the breast where the cancer actually was present.

So, there were, of those 25 cases, 50 films. Those 50 films were processed 10 times each on three different machines and then we assessed the scoring in the same manner as we did with the priors and the currents; did we hit the right area with the right mark.

We can see that for system one of the 500 tests, the machine marked the lesions correctly 500 out of 500 times; for system two 499 out of 500 times; for system three 500 out of 500 times.

So, within a system and across systems, the ImageChecker consistently identified the microcalcification and mass features. It is very reproducible both in and across systems.

As an overall summary of the study, we would like to conclude the following. The use of the ImageChecker does not result in any statistically significant increase in

patient work-up rates.

The ImageChecker system, based on review of those missed cases, or what might be considered likely to be missed cases, was able to play an important role in assisting the radiologist to minimize operational lapses by identifying areas on original mammograms that may warrant second reviews.

Finally, the system is highly robust and has an excellent sensitivity to the identification of calcification and mass features associated with cancers.

We believe that the mammography programs that are available in the United States are excellent for our screening programs and, as Dr. Castellino had noted, as Dr. Kass has noted, have made a tremendous step forward in the identification of early cancer.

We also believe strongly that the results of this study support our claims that the ImageChecker computer-aided detection system can make the screening process even better, by providing a perceptual aid to the radiologist performing a very complex task.

Thank you very much for your consideration and attention and we will be pleased to answer any of your questions. Thank you.

DR. ALAZRAKI: We will have time for questions during the panel's discussion of the presentation of the

company and then of the FDA.

At this point I think we will take a very short 10-minute coffee break and then proceed with the FDA's presentation.

[Brief recess.]

DR. ALAZRAKI: We would like to resume the meeting at this time. I would like to just give you a brief outline of the plan for the remainder of the meeting.

At this point the FDA will make its presentation of its review and considerations of the submission of the PMA.

Following that, the company will have a maximum of 15 minutes to respond to any concerns raised by the FDA or clarifications.

Following their clarification session to the FDA's presentation, the FDA will have a maximum of 15 minutes to respond to any issues raised by the company.

At that point, we will probably be ready for a lunch break. Following the lunch break, the meeting will be turned over to Dr. Romilly-Harper, who will lead the panel discussion.

During the panel discussion, the panel will be able to interrogate the company and/or the FDA and clarify its questions and concerns.

Without any further ado, Mr. Robert Doyle is the

FDA's review team leader for the PMA, P970058. He will provide an introduction of the PMA from the FDA's perspective, and during the FDA presentation, the executive secretary's duties, which Mr. Doyle also holds, will be performed by Ms. Nancy Pulowski, the Office of Device Evaluations panel coordinator. Mr. Doyle?

Agenda Item: OPEN COMMITTEE DISCUSSION: FDA Presentation on P970058.

MR. DOYLE: Good morning, Dr. Alazraki and the members of the radiological devices panel. My name is Bob Doyle, as Dr. Alazraki said, and I am a reviewer in the radiological devices branch and the lead reviewer for this PMA.

What I would like to do this morning is give you an overview of this submission from the FDA's viewpoint and highlight some of our findings.

As you are probably aware, the device now is a computer-aided detection system with image analysis and visual display capabilities intended for use as an aid for radiologists reading routine screening mammograms.

A condensed version of our intended use for the device, as we see it, is the device is intended to identify regions of interest on a mammogram using proprietary signal processing algorithms that superimpose markers on a video display, to bring those regions of interest to the attention

of the user after he or she has completed the normal reading process.

The study goals for this PMA, there were three primary goals. They are: it does not result in a significant increase in the number of patient work-ups; it improves the overall sensitivity of mammographic screening, overall meaning the combination of the device and the radiologist; and it reproducibly marks those regions of interest; those that are, as we see it, the primary goals of this study.

Now, the review team here at the FDA consisted of myself, two clinical reviewers -- Dr. Andy Kang and William Sacks. Technical performance was evaluated by Dr. Robert Jennings, we also had the statistical analysis and software analysis performed by the individuals performed there, a GMP review, a labeling review, and a BIMO review.

The general findings from those reviews were as follows. The GMP inspection was performed on April 3, and the company was found in compliance with all the necessary requirements.

The software as submitted, the information submitted about their software, was sufficient to meet the software concerns for a device at this level of concerned.

The BIMO documentation submitted was satisfactory, including certifications of device usage per the protocol.

The labeling itself we expect to finalize after we receive the input from the panel today.

From the standpoint, there are no electrical or other safety issues found with the device.

In addition to myself, the technical performance will be reported on by Dr. Robert Jennings, following myself, and that will be followed by the clinical study evaluation by Dr. Sacks.

I will mention to the panel that all of the other members of the team who were mentioned on the previous viewgraph. When the panel discussion takes place, if you have any questions for others, other than those making presentations, feel free to ask them, because they are here and can answer those questions. So, with that, Dr. Jennings.

DR. JENNINGS: In our evaluation of the technical performance of the device, we looked at certain hardware issues, we looked at those aspects of the algorithm, development and testing process that don't relate to the clinical tests.

We looked at the repeatability and precision of the device -- you have already heard about that -- and we also looked at the availability of measures to make sure that the thing continues to work in the way it is intended when it is deployed in normal clinical practice.

There are a number of hardware issues. This is actually a fairly complex device. There are two that affect the clinical use of the device, and I will concentrate on those.

The first is the characteristics of the film digitizer. That controls the quality of the information that goes to the algorithm.

The device is a high resolution device. It has a nominal 50 micron spot size. It has a long gray scale, 12 bits or 4,096 gray levels, so it has excellent gray scale resolution.

It has a large dynamic range. It can deal with films with up to a 4.1 optical density. So, it is capable of dealing with the high densities that you find on current mammography films. The bottom line is, we consider it appropriate for the job.

The display system uses two -- actually four, I guess -- small video monitors, the five-inch size, which already compromises their ability to provide high resolution information to the viewer.

In addition, the image that is displayed is seriously subsampled down from 36 megabytes to about 190K.

We concur with the company's statement that in order to review the case, after seeing the results of the ImageChecker, the radiologist is obliged to go back to the

original films.

In looking at the algorithms, our goal was to see that there was a rational development process and not to look for verification. That really can only be done with clinical material.

The algorithms are proprietary. The company provided a description of exactly what they do in layman's terms. They asked that we not describe that in any detail for the panel members. It is in your material.

The algorithms use a combination of conventional image processing and neural net techniques. As I said, the are not amenable to analytic evaluation.

The company did not provide a detailed description of the software implementation of the algorithms. In fact, in considering devices of this type with other applications, we have not asked for that information. So, this is consistent with our process.

The algorithms are trained and tested with a set of truth cases developed by the sponsor. These consist of about 100 microcalcification cases. These are biopsy proven cases with marks by radiologists indicating the location of the lesion.

There are about 300 mass cases, and these are used in training and testing of the algorithms. I guess the bottom line here is that there are no surprises. The

results that are obtained in the testing phase are consistent with the clinical results, and the overall method is quite reasonable.

The final point is that as far as we can tell, the current algorithms were frozen before the start of the trial here. So, there was no change in the algorithms during the course of the study.

What you see here is the results of what Dr. Stein presented as study 3-B. The bottom line is that we consider this reasonable proof that the system is fairly robust.

In series production it is always going to do the same thing as well as in repeated evaluations of the same film. So, we concur with the company's conclusions in this regard.

Especially with NQSA, now quality assurance is an area that we wanted to make sure was addressed by the company.

In looking at the performance of the digitizer by itself, there are resolution and gray scale test films that are available from Loomscan, the manufacturer of the digitizer, so they can check those aspects of the device.

The performance of the processing unit can be verified by running the algorithms on test cases that are supplied with the device.

Overall system performance can be checked by

scanning copy films, which are copies of, again, biopsy proven cases.

The films are scanned, processed by the algorithms, and then the marks are compared in software with the known locations of the lesions on those films to make sure that the identification is there and that it is correct within some small margin of error that accounts for variations in the way the film was digitized.

In summary, we think the hardware is appropriate. The development of the algorithms follows a reasonable process.

One point here is, at one point the company looked at the repeatability of the system using images of phantoms. They found that the phantom did not represent the kinds of things found in a breast.

Not only in algorithm development and clinical testing, but also in quality assurance, you need clinical case material to test these things, and the company provides it.

There are additional technical aspects of the device. As I said, it is fairly complicated. From our point of view, those have been addressed in the software and GMP evaluations.

DR. SACKS: Good morning. I am Bill Sacks. I am going to give the clinical presentation for the FDA. Just

for background, I am a radiologist, in addition to having been a physicist.

I have read thousands of mammograms and I had the opportunity about three weeks ago at the ACR breast conference here in Washington to actually see the device and to use it.

I actually did put my finger on the button, press it and watch these things come up. So, I have some experience with it.

Some background. Some of this was already covered by Dr. Castellino. I am going to cast it slightly differently, but you will see that it comes to fairly similar conclusions.

It is generally estimated that the sensitivity of screening mammography in the United States is approximately 80 percent, meaning that there are about 20 percent false negatives, which as we have seen, tends to be those that, when you look back at a prior mammogram when a cancer is discovered, you see that, uh-oh, it was there.

What that translates into, given that there are about 180,000 women a year in the United States who are diagnosed with breast cancer, that means on the order of 36,000 women represented by that 20 percent, whose cancers are missed and whose diagnosis is, therefore, delayed.

As Dr. Kass pointed out, and as we are all well

aware, when you delay a diagnosis there is a concombinantly higher mortality.

Again, Dr. Castellino pointed out that the top paper by Thurfjell in Sweden in 1994, they showed that when mammograms were double read, it increased the sensitivity on the order of eight to 22 percent over what we would start by estimating at about 80 percent.

A confirmatory paper that was done by Craig Beam in 1996 gave a similar range of about 8 to 14 percent improvement in sensitivity.

What that translates into down below -- I am going to minimize the mathematics here, but if you bear with me for a second -- if you start from the assumption that there is about an 80 percent sensitivity overall, that the 8 to 22 percent in the first paper, is 8 to 22 percent of that 80 percent, which means that there is a gain of 6 to 18 percent, meaning that sensitivity by double reading would go up from 80 percent to anywhere from 86 to 89 percent.

The Beam paper gives similar figures, that would go from 80 percent up to 86 to 91. Bear those ranges in mind as we come to our conclusion later.

Now, double reading offers an advantage, of course, that a machine can't quite -- not a machine of this type.

Of those false negatives in screening mammography

-- which as we said represents about 20 percent of them -- on the order of half are errors of detection. That is, the radiologist failed to see it. About the other half are errors of interpretation; saw it but didn't think it was anything to worry about.

This is from a paper that is actually a review paper of a number of studies and it varies from half and half to 60/40 and so on, but we get some idea that the 20 percent or so of false negatives are split somewhat down the middle between errors of detection and errors of interpretation.

Now, a second reader can correct errors, both of detection and of interpretation, whereas a device such as the M1000 is not capable, properly used, of correcting errors of interpretation, but only errors of detection.

Therefore, if it were perfect, it would get us halfway from the 80 percent to the 100 percent, or on the order of 90 percent.

We don't expect from a device of this type that it can increase the sensitivity of mammography to 100 percent.

Against that background, we will see how well it does. Before I get to that, I want to distinguish a device of the M1000 type which is a computer aided detection device from other kinds of devices which are also in development, which are computer-aided diagnostic devices.

We have heard of the term CADEX, and that would apply to the second column.

The difference between these is that the M1000 type, the detection one, is designed to increase sensitivity.

That means, of course, decreasing false negatives or decreasing missed cancers, whereas a device of the differentiation type would be designed predominantly to increase specificity and could also, under certain circumstances, increase sensitivity as well.

What that would mean would be to decrease the false positives or decrease biopsies of what I call LTBs -- that is, lesions which turn out to be benign, to avoid phrases such as unnecessary biopsies or biopsies of benign lesions.

After all, a judgement of benignity is one made after the fact and it can't influence what you decide to do ahead of time.

Detection types like the M1000 scan the whole image and, indeed, can be used on the entire screening population -- that is, on every single screening mammogram.

Diagnostic types scan a portion or portions of the image that are selected by the radiologist and the device is then queried by the radiologist, do you think that this is benign or malignant.

It is used only on that subgroup of films that are selected by the radiologist.

It is important to note that the M1000, in this column, is not designed to different between benign or malignant. It is merely to see if, as has been pointed out, there are regions of interest that the radiologist failed to notice.

It therefore just corrects errors of detection while the differentiation type can correct errors of interpretation.

Indeed, one can imagine making a device that combines both these features and renders mammographers obsolete. That is why I came to the FDA. [Laughter.]

Now, this is a simplification and reduction of a four-dimensional four-by-two-by-two table that I am going to walk you through.

I don't have everything on here, but this will allow us to summarize, from our point of view, some of the issues that have been raised.

If we start from the point of view of the radiologist, each lesion is either seen or not seen by the radiologist.

Under those that the radiologist did see prior to using the ImageChecker, the radiologist will have either decided to work it up or not to work up that particular lesion.

Then comes the device itself which either marks or doesn't mark. That would be the marks represented by this row and the no marks represented by this row.

Now, the whole purpose of this device is in the area where this heavy arrow is. That is, it is designed to take those lesions that the radiologist did not see, mark them, and cause the radiologist to go from a state where they would not have worked it up, naturally, because they didn't see it, to one where they would work it up.

Of course, that will always include true positives and false positives. There is no way to avoid false positives when you have true positives.

Similarly, if the radiologist already saw the lesion, and had decided not to work it up, there is a theoretical possibility, just indicated by the dashed arrow here, that if the device marks the lesion, it could cause the radiologist to change his mind, and the theoretical possibility that if the lesion is not marked and the radiologist was originally going to follow up on it, that it could cause the radiologist to change their mind and decide not to work it up.

I only mention these for the sake of completeness. There are, in fact, two protocols, the first two studies that the company did.

Protocol two, as you have already seen, was

designed both to see how much the device was capable of taking those that the radiologist didn't see and moving them not only into a did see but a decision to work up a lesion -- that is, increasing the sensitivity of mammography.

Indeed, even if the radiologist did see it, decided to work it up but there was no mark on it, some of the radiologists that were ejected from the protocol might be those that might say, uh-oh, the device didn't mark it; maybe I shouldn't work it up, and it could drop the sensitivity.

Protocol II would also cover that. The net effect, as will see, showed that the net effect was a gain in sensitivity.

While there may be a few of these for some radiologists, in my opinion, such radiologists should not be allowed to read mammograms.

Similarly, when you do change from a no work up to a work up situation, whether you saw it or not, the question that we asked the company to deal with -- and which was dealt with in protocol I -- was is there a significant number of call backs.

Now, a call back, of course, means that you are looking at the four views of the mammogram on a Tuesday that were taken Monday afternoon.

The woman is long since gone and you see something

that you think is questionable. It is probably a super position of shadows, but you are not sure, and you want her to come back because you want to take an extra view.

You do it on Thursday and you say, oh, yes, it was just a super position, and she is fine and she goes home.

That is, after all, and the company's protocol I was designed to see that that was not an excessive number.

Something has been made in The New England Journal of Medicine about a month ago, of these false positives in mammography and said that over a 10-year period, about 50 percent of women will get a false positive.

That article did not distinguish between a call back such as I just described and a biopsy. In other words, there are many levels of false positive. At that, they exaggerated the number. I think it is important to keep this distinction in mind.

In any case, protocol I, as we will see, showed an insignificant number of increases of total call backs as a result of the device marking a lesion.

Now, I am going to give you a little walk through this somewhat complicated diagram. From it, I think you can see everything you ever wanted to know or didn't want to know about sensitivity, specificity, positive and negative predictive value, and we can see where we are coming out with the M1000.

This line here represents all screened women and this vertical line is the border between those with cancer to the left of it and those without cancer to the right of it. That is the underlying ground truth, cancer and no cancer.

This line is broken up, because in screening mammography those with cancer, as Dr. Castellino pointed out, represent roughly .4 to .5 percent. We have seen estimates as high as .7, but it is less than a percent, which means that this line is 100 to 200 times as long and would go way out over there, so I have broken it up.

This box represents the positive, the true positives to the left of the line and false positives to the right of the line; that is, one that the radiologist would say, this looks like one; I want to work this up.

I am also using the same graph to stand for any stage of this; that is, a positive even down to the decision to biopsy.

The purpose of the M1000, the intended use here, is to increase this true positive rate up to the left, to add this increment of delta TP.

That is the purpose of the device and we will see how well it does in a minute.

This is sort of roughly to scale. That is, beforehand it is about 80 percent of all the cancers are

found and it is designed hopefully to cut that false negative rate in half, by changing half of those false negatives to true positives.

Now, the definition down here at the bottom of sensitivity is nothing more nor less than the proportion of all cancers that true positives represent; that is, it is about 80 percent of this whole area here, the TP over the sum of TP plus FN.

Specificity, on the other hand, can also be seen off of this diagram. It is merely the percent of all negatives -- all those women without cancer -- who are called negatives, the true negatives.

That proportion is a very large proportion because this line is very long and it is that proportion of the total non-cancers that are called negative. Therefore, the specificity is the true negative over the true negative plus false positive.

Along with the increase in true positives, as I pointed out on a previous slide, there is always necessarily an increase in false positives.

That is, before the ImageChecker, we may get a positive rate that looks like the inner box here. These are the call backs without the M1000.

Then with the M1000, it gives you an increment that increases both true positives and increases false

positives with a delta FP.

The protocol I was designed to see, is the total of delta TP and delta FP -- that is, the increase in both true and false positives -- a statistically significant number.

The answer, as we saw from the company's presentation, was that it was not. As a matter of fact, it actually dropped slightly from before installation to after, and all that does is indicate that the noise, the statistical fluctuations, swamped whatever effect the ImageChecker had in increasing the number of call backs.

It is the intent of the M1000 that it increases the number of call backs. If it doesn't increase the number of call backs, it is not doing its job.

Therefore, the only question is, does it magnify the number of false positives so greatly that we are dealing with an outrageous increase.

That was the question we asked the company to demonstrate, which they successfully, in protocol I, demonstrated that it did not do.

It is impossible for us to say by what extent the device actually was responsible for increasing the number of call backs, because there is just so much noise there that we can't pull the signal out of it and we are convinced that would also be the case in clinical practice.

On the other hand, we also feel that is a secondary issue. The primary goal of screening is to increase true positives; that is, to increase sensitivity.

Carl Dorsey, three weeks ago at the ACR breast conference, made the comment that underscored all of that. He said, he has a way of guaranteeing that when he reads mammography he is better than 99 percent accurate. That is, all he has to do is call every single mammogram negative.

Ninety-nine-plus percent are negative, and he would be right all that time. He would, of course, detect no cancers, which just exposes the silliness of the article in the New England Journal.

The goal is to detect cancers. If we get some extra false positive biopsies in here, that is the price we have to pay for protecting those cancers.

Certainly, all they were dealing with was the number of extra call backs and that, too, is a very small price to pay.

We do not belittle that issue, but the company demonstrated that there was not a significant increase.

Now, positive predictive value is what is really much more important in mammography or almost any screening test than specificity.

Positive predictive value is, of all positives, what portion are true positives. That is, what portion of

all positives here actually have cancer.

As I have demonstrated, it looks on the order of 20 to 30 or 40 percent, which is what we find in screening mammography today.

I have drawn that roughly to scale. At the lowest level of recommendations for biopsy, about 20 percent, give or take, turn out to be cancers and about 80 percent turn out not to be cancers.

Positive predictive value is the main issue. Even if delta TP and delta FP are significant, the question is, does the ratio of the new true positives to total positives still maintain its 20 to 30 percent.

It does, indeed, because these turn out to be lost in the noise. Just for the sake of completeness, negative predictive value is the percent of all those that are not called cancer -- namely, this part of this line, and this part over here -- that are in fact not cancer.

So, it is TN over TN plus FN. That is negative predictive value.

Of course, for screening mammography, since TN is huge, the negative predictive value is well over 99 percent.

Now, this is the table that the company has already shown you. It is the number of cases correctly marked, in the third column, of all of those that were judged by the panel radiologists to require further work-up.

Any lesion -- 83 of the lesions, none of those radiologists would have picked out. Of those that only one picked out, there were 53, and so on and so forth.

What this demonstrates is, as Dr. Stein pointed out, that the closer you get to the bottom of the chart, first of all, the more conspicuous the lesion must be.

If five out of five see it, that is an indication of conspicuity. At the top it is subtlety.

Similarly, the farther you get down toward the bottom of the chart, the more suspicious something looks, because this is the number that the panel of radiologists would call for further work-up.

It is not just that they noticed it, but that they think it is suspicious enough to need further work up. The more radiologists out of five who think that is the case, clearly the more suspicious it is.

As we will see in a minute, there is one other thing that this scale actually indicates, and that is the likelihood that it would be worked up, and we will come back to that in a minute.

As Dr. Stein pointed out, the device is more sensitive for calcifications than for masses. I put quotes around masses, because as they pointed out, everything that wasn't a calcification was called a mass.

It is capable of picking up, as Dr. Castellino

pointed out, architectural distortion, and that is also put in this column.

As we saw, anywhere from 95 to 100 percent at the low end of the chart, of calcifications are picked up. It is very sensitive to calcifications, and masses it is quite impressive as well, 74 to 87 percent.

Now, this is that same chart I showed a second ago but adjusted. In the last column I have adjusted the number that are correctly marked by the M1000 for the likelihood that these would be worked up.

The likelihood is proportional to that proportion of radiologists who decided that they would work it up. In other words, if you had a lesion that only one out of five would work up, that is a 20 percent probability that it would get worked up, is the way I looked at it.

This is another approach. It is an alternative approach to the way that the company looked at it. They just took the lower end here.

I am going to take the entire chart and show you that we get essentially the same results.

If you take the 28 that were correctly marked by the M1000, multiply it by 20 percent, you get 5.6, and so on.

This last column represents nothing more than the product of the first column and the third column. If you

add all of those up, you get 89 out of the 286 total priors that the designated radiologist felt showed the lesion on the previous mammogram.

Now, if you look at the top row here -- this is an interesting row -- none, zero out of the five panel radiologists found this lesion.

Yet, 83 such lesions were included by the designated radiologists as opposed to the blinded panel radiologists. It always makes me shiver when I hear the term blinded radiologists.

I am also uncomfortable about the fact that I am wearing glasses and neither Dr. Castellino nor Dr. Kass is, which is why, again, I work for the FDA.

None of the three that the panel radiologists picked up, but were said to be visible priors by the designated radiologists, one might question whether they were really visible priors.

Understand that the designated radiologists were not only not blinded, they knew exactly where the lesion was and they were knew it was a cancer.

The retrospectoscope is a very, very powerful device, much moreso than either a magnifying glass or the M1000.

It is amazing what you can pick up with it, and there is a tremendous bias when you look back at a mammogram

that you know that was a cancer.

So, one might reasonably even scratch this whole top row of 83 and say they were not visible priors. If we subtract 83 out of the total 286, we have a total 203. So, 89 out of 203 is actually a higher percentage.

I have done the calculation both ways, just to bracket it. If we take the 89 out of 286, that is 31 percent.

That is, of the false negatives on the prior mammograms, the device would have the radiologist -- first of all, would point out and the radiologist would have worked up 31 percent of those false negatives.

If we scratch that first row, then out of 203, instead of 286, that would have been 44 percent of the false negatives.

So, you get a bracket somewhere between 31 and 44 percent of those 20 percent of false negatives on mammography that this device would not only point out but would actually have the radiologist actually working up as a result of the devices pointing it out; that is, devices that they would have not seen.

We have, then, if we say that mammography without the M1000 is approximately 80 percent sensitive with 20 percent false negatives, and the device can give us a 31 to 44 percent reduction in those 20 percent of false negatives,

then 31 to 44 percent of 20 is 6 to 9 percent -- that is, it is changing false negatives to true positives.

That would change the 80 percent to 86 to 89. If you will remember the figures we saw in the early slide of what double reading does, it was 86 to 98 or 86 to 91, and the device is capable of giving us an 86 to 89 percent sensitivity.

Again, of course, there are assumptions in these figures, namely that there is an 80 percent sensitivity to begin with.

If you are dealing with a radiologist whose individual sensitivity is already 95 percent -- and Craig Beam has done a number of studies that show that there are such birds -- the fact is that their increase in sensitivity will be almost negligible, because how much closer can you get to 100.

So, we are talking, on average for the entire group of radiologists in the country who are NQSA certified -- and that covers a multitude of sins -- we can expect to get up to about an 86 to 89 percent sensitivity.

So, in summary, first of all, given that most radiological practices do not do double reading, and that managed care tends to prohibit its adoption because of the concentration on cost, the potential contribution of the M1000 to the overall sensitivity of screening mammography

appears to be significant.

The M1000 allows a 31 to 44 percent reduction in false negatives with an increase in sensitivity from 80 percent to 86 to 89 percent.

What that translates into is 11,000 to 16,000 more women diagnosed earlier than they otherwise would be, of the 36,000 that are missed.

Third, the loss of specificity due to the use of the M1000 -- that is, the increase in false positives -- appears to be small enough that there is no significant decrease in the positive predictive value of biopsy recommendation. Thank you.

DR. ALAZRAKI: Thank you, Dr. Sacks. At this time the FDA has completed its presentation. R2 may have up to 15 minutes, if they wish, to either clarify any issues or present any additional information, query the FDA.

DR. STEIN: No, no thank you.

DR. ALAZRAKI: I presume, therefore, that none of the members of the FDA -- does anyone in the FDA wish to query the company?

In that case, it is now only 11 minutes after 11:00. I think it is perhaps a little too early to break for lunch.

What I would like to do is turn the meeting over to Dr. Romilly-Harper, who is going to run the panel portion

of this meeting.

Dr. Romilly-Harper and Dr. Judy Destouet were both designated as primary reviewers for the panel for this submission.

Agenda Item: Panel Discussion.

DR. ROMILLY-HARPER: Thank you. First, I would like to tell my fellow panel members that I thoroughly concur with Dr. Sacks' review of the system.

As a diagnostic radiologist, one of our major problems is detection when we look at screening mammograms.

Interpretation, we can usually do something by means of intervention and training and improve that aspect of it. It is detection, even in the best of hands, that continues to be a problem.

I would like also to congratulate the company on the protocols that were used to evaluate the system, in that I think they were specifically designed to answer the questions that a typical radiologist would like to ask.

In that vein, however, one of the major things that we will talk about later specifically is labeling. One aspect that I would want to caution the average radiologist is not to think of this as a panacea for 100 percent detection of breast cancer through screening mammography.

With that in mind, I think that labeling issues have to be specifically looked at in the fact that

radiologists need to be aware that the system has not been designed to specifically look at increasing opacities.

Also, areas of minimal potential distortion, such as skin thickening or skin retraction or stuff will be not specifically addressed by the system. It may or may not, but it might be a chance issue.

With that in mind, I think the panel members could maybe address those issues later. I would like Dr. Destouet to make her comments on her evaluation of the product.

DR. DESTOUET: I think the manufacturer did a wonderful job in thoroughly evaluating all aspects of what the typical radiologist encounters in the screening setting.

I have a couple of questions, one of which is for Dr. Kass, if she could come to the podium, please.

As you demonstrated very well on the slides, the digitized image is not of the same quality in contrast, certainly, as compared to the standard high quality mammogram images that we interpret in our screening programs.

Did you find that to be detrimental to your evaluation of the lesions that were marked by the ImageChecker?

DR. KASS: No, I did not. The digitized images, when you bring them up by touching the white button after you have finished looking at the real analog mammograms,

they are located, usually, directly below the corresponding film from the mammogram.

It is a very easy thing to learn to, you look down at the digitized image. You see a mark. It registers in your mind as where is that mark spatially relative to the entire breast, relative to obvious features of breast parenchyma.

You move your eyes up. You look at the mammogram and it just locks in, in your mind. I think most radiologists should have the basic perceptual skills. It is real easy. You just look right up.

DR. DESTOUET: So, once you saw a mark on the digitized images, you looked at the mammogram film.

DR. KASS: Yes.

DR. DESTOUET: And your analysis, then, of how to proceed with that marked lesion was based on the mammogram, not at all on the digitized image.

DR. KASS: Right. The digitized image is just a locator, drawing my attention to a region of interest.

DR. DESTOUET: Did you ever wish that there was a way that you could change the contrast, or that you could magnify the digitized image? I am just asking.

I am putting myself in the setting where I did not perceive something on the original mammogram. I look at the digitized image. There is a very subtle finding. Some of

the things that obviously were demonstrated were very subtle findings.

I wonder if there is a way to manipulate the digitized image if that would help, or did the manufacturer specifically design the system so that that did not happen.

DR. STEIN: That is not possible to do. The subsampled images do not have any information available to the radiologist that would be at the resolution available in the original film.

There is no other button to hit. There is no way to zoom in on that digital monitor. As was mentioned, we go from 30 to 40 megabytes per film, 160 megabytes a case, to a couple hundred kilobytes for a low resolution image.

At that size, usually the feature, in and of itself, is obscured by the marker, even where it would be.

The point is that the images themselves that are presented on the mini-monitors are of such low resolution that there is nothing that we actually provide in the files that are transferred over to the display unit, for the radiologist to even have access to.

The high resolution images would actually absorb so much data at 160 megabytes a case, that there would be no place to store all that information.

There is only the subsample image. I was trying to additionally point out, the markers on the minimonitors,

if there is a calcification, I don't think you can even usually have a hint that there is a calcification on the low resolution image. You have to look up. You have to look up to the film.

DR. DESTOUET: Dr. Kass, did you find in your clinical evaluation of the system, that there were cancers that you saw on the routine mammogram image that were not indicated on the digital image, and therefore, you did not look up.

I know it is anecdotal, but I am sure you have looked at that data.

DR. KASS: In our department, what we were looking at was screening studies. Right from that, you take away very, very large, palpable masses.

I think in the experience of most of the people in my department, when we see a cancer, we pretty much expect to, when we hit the white button, have a mark come up on it.

I really can't think of any cases off-hand where a cancer was not marked, in our experience.

DR. DESTOUET: There clearly are areas that the ImageChecker, as Dr. Romilly-Harper pointed out, that the algorithm is not designed to find.

DR. KASS: Correct.

DR. DESTOUET: Architectural distortions which can, indeed, be very subtle, developing densities that,

indeed, can be very subtle.

In your experience, such lesions like that were not missed because the ImageChecker did not mark them.

DR. KASS: The ImageChecker is designed to look at an individual film, and identify features on that film that need the radiologist's attention.

It is the radiologist's part, or it is part of the radiologist's job to look at the image, as an isolated image in time when compared to a prior -- is there anything that is developing here -- and as an image in space, contralateral breast asymmetry.

At this point, the ImageChecker does not deal with priors and it does not deal with contralateral breast for asymmetry.

DR. DESTOUET: So, in your typical viewing situation you had prior mammograms and the current mammograms you were interpreting and then the ImageChecker image below.

DR. KASS: Correct.

DR. DESTOUET: Did you find that the other marks -- there were 1.8 marks per cancer case, 0.9 marks per normal cases. Did you find some of those markings to be a handicap?

DR. KASS: The learning curve for this is very rapid. I found that it was very, very quick in the learning

curve that I would become accustomed to what marks would appear that were common findings that I would not have to worry about.

Skin calcifications is an example that comes to mind, areas of summation. For an experienced radiologist, it is usually very simple and not time consuming to go back up, make sure that you haven't missed anything, make sure you haven't failed to perceive anything important in that area, and that you can explain why there is a mark on that spot.

It is skin calcifications, it is summation, things that fit into the benign as opposed to the not benign category.

DR. DESTOUET: Thank you. I have just a couple other questions for Dr. Stein, please. It is clear from the analysis of lesions that the ImageChecker marks, it is very good with microcalcifications. It did less well with masses.

Of the lesions, of the masses where there was either a super majority or a high majority of radiologists who identified the lesion, was there a difference in the appearance of the masses on those cases between the ones that the ImageChecker found and the ones that the ImageChecker did not find. Did you analyze those lesions?

DR. STEIN: This is a very interesting question

because it does beg many of the linguistic differentials between what you as radiologists do as compared to what machines do.

The machine is identifying, remember, a density and is looking for radiating lines, which is not necessarily the same as what you call spiculations.

Those retractions are more prevalent than you may realize in the images. Therefore, we see linear structures and densities much more commonly than you would expect.

So, for instance, when you use a language and say, these are asymmetries, the machine doesn't even know asymmetry. It doesn't do any left/right comparisons. It only looks at any individual film.

It may have hit what you called an asymmetry, but not because it was asymmetrical, but because of an intrinsic characteristic of that lesion on the film.

Now, when we looked at the higher consensus cases, from the machine's perspective, these were cases of higher and higher probability where there was stronger density and stronger radiating line features.

Again, the language issue, I am not going to say these were all what you would call spiculated masses, because actually I don't even know what you all regularly call spiculated masses.

We have seen too much language variability in the

radiologic community when we see a density with some spiculations.

Some people will say that is an irregular margin and some will call it stellate and some will call it -- we couldn't actually create that language in the claim, so we tried to leave it at the level of mass and calcification.

As Dr. Castellino demonstrated in one of his slides, the machine itself sees features that do range from densities to densities with spiculations in your language. We have a better chance of hitting those, the more they fall on the continuum from pure certain strength densities to those that have strong spiculations. Does that help at all?

DR. DESTOUET: It is going to make it difficult in labeling, I think, because one of the things we clearly want to make known to the radiologists in general is, as Dr. Romilly-Harper pointed out, this is not a panacea. There clearly are some lesions that will not be marked.

If we talk about stealing time from cancers, the ones that we want to steal time from are those spiculated masses that, indeed, can grow very quickly, and from a stage I to a stage II cancer over a year's time.

If there was some analysis of those lesions that, indeed, may not be routinely marked, it could help us in labeling.

DR. STEIN: To that end, the company has, in its

labeling for training purposes, it provides not only an operator manual on the processor, on the display unit, but provides something that you might have noticed in the algorithm description book.

That algorithm description book has many film examples, between 50 and 75 cases of film examples of types of calcification structures that are hard to hit, types of structures that are marked as calcifications that are really calcifications in vessels or crossing structures, and similarly masses that are hit and the types of mass lesions that are not hit.

We can only do it by example because we don't know how to create a fundamental classification system in this area.

DR. DESTOUET: So, there is a teaching set or a learning set for radiologists?

DR. STEIN: Yes, Dr. Destouet.

DR. DESTOUET: My last question is, do you have a breakdown of the stages of cancer detected by ImageChecker?

DR. STEIN: No. What we do have -- I don't know if this is exactly a response to that, but we are not sure that we have consistent enough staging information because the surgical and biopsy reports are often not as complete, or the women might have had a biopsy one place and surgery someplace else.

What we actually do find is, of course, we have collected this material from 1,083 cases, particularly the sensitivity numbers. One would clearly expect that the full range of size and distribution and stage of lesions that you would expect out of 1,983 cases should be represented in this data set itself.

DR. DESTOUET: I understand, but this is a screening population. If anything, you should be closer to the stage zero, one and two, I would expect, since you eliminated all palpable lesions.

DR. STEIN: This is absolutely correct.

DR. DESTOUET: So, you are talking about a screening population. So, you really don't know what stage cancers were detected by ImageChecker versus --

DR. STEIN: We do not have stage information on these cases.

DR. DESTOUET: That may be something interesting, or not just interesting, but something that the FDA would want to know.

DR. ROMILLY-HARPER: Any other questions by the panel members or issues?

DR. ALAZRAKI: I would like to ask Dr. Sacks if you know how many second readings of mammograms are done today in the United States as a routine.

DR. SACKS: No, I don't know the figure, but I

know that in Craig Beam's article it was very, very small. It was less than 10 percent, by a good margin.

DR. ALAZRAKI: Another question, Dr. Sacks, I don't know if you are the right person to ask in the FDA, but once approved, a product such as this, what process does the company need to do to change their algorithm or to make any changes to the product?

MR. DOYLE: I can probably answer that. They have to submit what we call a PMA supplement for any changes they make in the device. That goes on indefinitely, for as long as they have this device on the market.

DR. ALAZRAKI: So, any modification of the algorithm or additional information that would be provided by the algorithm would have to come through as a supplement application.

MR. DOYLE: That is correct.

DR. MALCOLM: I have a question, because it wasn't mentioned -- I am not sure if I remember reading this. How is this image stored? I am really talking about the future?

If the radiologist has looked at the mammogram, looked at the checker, made a decision on work up, you know how the circle goes. I am from California, particularly.

The question is, what happens to the image and what are the legal ramifications?

DR. STEIN: In terms of copy, there is a drive

from where the images are transferred to in the display unit. Those units are over-written as new cases come in.

If the operator wants to save a copy of that material, they can make a hard copy printout on our laser printer.

We do not normally save or append it to any information. As far as medical legal, I am unqualified to comment on that.

DR. SMATHERS: Would you please go back to the podium? Now I am confused. How many films do you scan in and hold in storage at a time?

In a busy clinic -- I don't quite see or follow how the data is stored and then essentially destroyed or overwritten.

DR. STEIN: I believe the number is the disk can hold 2,000 to 3,000 cases before we start to overwrite.

DR. SMATHERS: Is there a way to back up those tapes on a routine basis so you could store that and keep an archive?

DR. STEIN: We have not made that. We can do it. We have not made it a part of the system. If you want to maintain those ImageChecker printouts, then you literally would print them out as paper copy.

DR. SMATHERS: May I ask one other question? I think you pretty well have handled that. There is

absolutely no way that a creative technician could get in there and mount a couple 17-inch high resolution monitors above your standard display system and get a high resolution image from your system displayed up there, of the ImageChecker system?

DR. STEIN: The file that is transferred, the data is not there. The 160 megabytes that would be associated with digitizing a case is never transferred and that is not saved at all.

DR. SMATHERS: One last question. Is there any sensitivity at all about the way the image is put through the scanner?

Say I flipped it 180 and got the orientation left/right wrong or something, or on a really bad day it was dropped in at 90 degrees off of normal orientation. Does your system respond properly or would they just have to reload it?

On some extreme versions I know that the machine will just tick out what we call a red border and a fault.

DR. O'SHAUGHNESSEY: Typically, on the front panel of the processing unit that the technologist can see, they see a very, very tiny, we call it a mini-picture of the image.

As they process it, they would see the red border. They would also see the image upside down. They are

instructed in the manuals to just load in that one film again and rerun it.

DR. SMATHERS: They are instructed in the manual, but most people don't read the manual.

DR. O'SHAUGHNESSEY: They do it because they can see it on the image. Also, the doctor, when they go to read the image, will notice that it is upside down.

DR. SMATHERS: So, your system requires a given orientation for it to function properly.

DR. O'SHAUGHNESSEY: Yes, it does, to properly show the image in the right orientation at the end.

DR. MALCOLM: I didn't see in the documentation, perhaps with all the different sites it is not an issue. Did you happen to notice any differences in the reading with regard to the manufacturers of films?

There are a number of different companies who produce X-ray film. Are there any differences or did they all come out the same or does your system take that into account?

DR. STEIN: The system actually formally takes that into account. There is a normalization that is run not only just for film, but to account for the differences in density that are present in the breast, which are much broader than anything in the film. So, that normalization step is the first pass of the algorithm. That is

transparent to the operator.

DR. ALAZRAKI: I don't remember if this was in some of the data, but what is the smallest breast cancer that you can mark with the R2 system or that you have marked with the R2 system?

DR. STEIN: I may defer to one of the docs in this, because how small is a calc? I mean, we are measuring on a 50 micron level. We can identify a calc at 50 microns.

In terms of the cancer, I don't know what that is, because the trigger for the threshold for marking is based on how strong a density and how strong a set of radiating lines are.

We did not formally measure all of the lesion sizes because we found that there was, again, too much variability in what constitutes the size of a lesion on a film.

DR. ALAZRAKI: Is it not also based on some clustering of pixels which have some threshold density?

DR. STEIN: On the calcification, I believe, if I remember correctly, the numbers will be you have to have at least three as described in the algorithm book.

Those individual spots that the system identifies as calcifications must each be within two-and-a-half millimeters of each other, at least.

DR. ALAZRAKI: Another question. On the 286

visible priors, you broke them out into microcalcifications or calcifications and masses.

What was the gold standard that you used to say this is calcification.

DR. STEIN: The original site radiologist defined on the currents what the primary feature, in their estimation, was of that lesion.

For instance, if they said they called it because it was a calc or a mass -- excuse me, a mass that had calcs in it, they would say that is a mass. Whatever they defined as the primary feature, that is what we called it and we pass through.

We also, of course, did note the secondary characteristics of the lesion if they were available. So, we covered both sides of it that way.

DR. ALAZRAKI: So, it was not a histopathological calcium designation.

DR. STEIN: No, it was a radiological.

DR. ALAZRAKI: It was an expert reading of what is calcium on a film several months later?

DR. STEIN: Yes.

DR. ALAZRAKI: Another point. What about patients who have had prior surgery or excisional biopsies. What happens to the performance in those patients?

DR. STEIN: There were 62 cases that had surgery.

Because we were trying to make claims on the basis of asymptomatic cases, and because so many institutions that we were involved with said these patients with prior surgery, or who were unilateral, they are automatically diagnostic.

We did run, of course, the ImageChecker on the unit. We hit over 60 percent of those, but we didn't report that formally in the PMA.

DR. ALAZRAKI: I am just wondering, in terms of the labeling, whether you maintain the same sensitivity to specificity type of ratio to women who have had prior interventions in the breast.

DR. STEIN: As I said, we didn't even attempt to claim on that level at that point with those 60 cases.

Similarly, Dr. Alazraki, since we excluded all the patients who were symptomatic, we were only looking at the women who may have been asymptomatic, currents who may have been defined as having asymptomatic screening mammograms.

That is where we said we can make the biggest help. But we do mark them. The machine doesn't know whether the woman had -- we only do one film at a time. It doesn't know whether the woman may have had a mastectomy or not.

DR. ALAZRAKI: In the 60-some-odd you said you looked at who had prior surgery, how many marks per breast were there, as compared to the .9 or 1.8 or 1.9?

DR. STEIN: I don't know the number of marks per breast off the top of my head.

DR. GARRA: I have a question going back to the size of lesions again. I think early on in your presentations you talked about wanting to get after the lesions that are a centimeter in size or less.

I notice in the algorithm description that you are optimizing for 10 to 20 millimeters in size. So, your algorithm is optimized for larger lesions -- not huge lesions, but somewhat larger than you might expect to want to go after in a screening population. I would like your comments on that.

DR. STEIN: I think it was Dr. Kass who said that the medical community would ideally like to catch cancers less than a centimeter, so that the opportunity of treatment of those women would be expected to be truly curative as opposed to having a high probability of survival.

The system, as you said correctly, it is optimized absolutely in the 10 to 20-millimeter area, but it is not limited to that area.

On the calcifications, as I pointed out, that is of course for the masses only. On the calcifications, it is all the way down to 50 microns. Does that help?

DR. GARRA: That is what is in the manual. Obviously, there might be some technical problems or

something to go to smaller size lesions?

DR. STEIN: I don't know. When we identified the densities, as also described in the algorithm description manual, we do the identification of the densities by putting in a sense, an annulus over the entire image that has a dimension of six millimeters.

We look for densities in that area. But the density that you can identify on an expert system is based on not just the intrinsic density. It is a matter of contrast difference, too.

So, we have, in our own test data base, tried to optimize those so that we would know that we would never miss those.

We have also captured larger lesions and smaller lesions, but we have not tried to quantify them because the algorithm, again, does not look at it as you do.

DR. ROMILLY-HARPER: Dr. Garra, do you need more clarification?

DR. GARRA: I don't think for the purposes of this. I mean, it would be interesting to know what went into the decision to optimize for that range, but it is not necessary for the purposes of the PMA evaluation.

DR. ROMILLY-HARPER: Okay, thank you. Dr. Griem?

DR. GRIEM: I wondered about ductal carcinoma in situ, and also whether you had any bilateral lesions where

both breasts were involved.

DR. O'SHAUGHNESSEY: I am Dr. O'Shaughnessey from R2 Technology. I was the manager of the clinical studies. We did have many cases of ductal carcinoma in situ. They were counted as part of the cases that we included in the studies.

Bilaterals, there were, out of the 1,083 current cases, on the order, a representative number of bilaterals. I don't know off the top of my head how many there were. I can recall several cases in my mind, but I don't know exactly how many there were. There were some.

DR. MALCOLM: I guess one more question of clarification, because I am trying to remember. I think when you demonstrated, I think, reproducibility in 499 out of 500 with the three machines, that was only on calcifications; is that correct?

DR. STEIN: Fourteen calcifications and 11 masses.

DR. MALCOLM: I couldn't remember.

DR. STEIN: Which were visible in both views. So, there were 28 films with calcifications in them and 22 films with masses.

DR. ALAZRAKI: I think everybody -- any more discussion from the panel? Mr. Doyle is going to put up some discussion questions and things that we will think about over lunch.

MR. DOYLE: Yes, I think since we are getting close to lunch but not quite there, I will put the questions up, read them, give you a chance to think about them, and then we will break for the closed session, which starts at 12:00 and then the panel can be prepared to discuss these after the closed session when we reconvene at 1:00 o'clock.

Let me put these up. I will quickly read these.

Please discuss whether or not you believe that the PMA contains sufficient data to conclude that the M1000 ImageChecker can reduce observational errors by identifying overlooked areas on the original mammogram.

If the device results in an increased sensitivity, is an increase in workups an important consideration.

Sort of tying into that, the third question. If you conclude the M1000 ImageChecker helps to minimize observational errors by identifying overlooked areas on the original mammogram, please discuss whether or not you believe that the PMA contains sufficient data to conclude that this can be done without unnecessarily increasing the number of patient work-ups significantly.

Please discuss whether the labeling of this device, including the indications for use, is appropriate given the data provided in the PMA, or should it be revised or amended with respect to the following:

Claimed ability to flag overlooked cancers;

relative ability to detect masses and calcifications; or any other characteristic or claim for the device.

Finally, are there any issues not fully addressed in the PMA. If so, should these be resolved before the PMA is approved, or can these ultimately be addressed by postmarket surveillance or a postmarket study.

Those will be discussed by the panel, as I say, starting at 1:00 o'clock. I think at this point we are a little ahead of schedule, but we are going to break for lunch.

DR. ALAZRAKI: We will break for an hour and a quarter in that case, and we will reconvene at 1:00 o'clock to discuss these FDA presented questions, the panel discussing these questions with consultation, if requested, by company and FDA.

Then following that discussion, I think we will be ready for a concluding motion. So, the session that we are having now is a closed session for the panel members. The public will have to vacate the premises.

MR. DOYLE: Yes, it is for panel members and selected FDA members. Thank you.

[Whereupon, at 11:45 a.m. the meeting was recessed, to reconvene at 1:00 p.m., that same day.]

A F T E R N O O N S E S S I O N (1:05 p.m.)

DR. ALAZRAKI: We would like to, at this point, call the meeting back to order. We would like to remind the public observers of the meeting that, while this portion of the meeting is open to public observation, public attendees may not participate unless specifically requested to do so by the chair.

At this point, R2 has requested a few minutes to respond to a couple of questions that came up during the panel session. We have agreed to allow R2, at this point, to make whatever additional response they wish.

DR. STEIN: Given the questions that came up in the last few minutes before we took our break, particularly those issues associated with sizing of lesions and classifications, during our break we also had a discussion about this.

Dr. Brown from Johns Hopkins and Dr. Cederbom from the Oschner Clinic, who have been very experienced with the device, would like to share some of their observations and comments on these matters.

DR. BROWN: I am Rachel Brown. I am the acting director of breast imaging at Johns Hopkins. I was involved in the early clinical data with the ImageChecker, and I would like to point out several things.

Firstly, my impression with the cancers --

DR. ALAZRAKI: Can you just state your connection to the company and whether they are supporting you.

DR. BROWN: I was compensated for my time for doing the study and my staff, the time spent doing the study as well. They have supported my trip here today.

DR. ALAZRAKI: Thank you.

DR. BROWN: My experience with the ImageChecker is that there has been no specific characteristic of the cancer that was not detected, that it was not size alone.

I can say that my own experience has been that I have been very amazed sometimes at how subtle some lesions are and surprised at some others that I would have thought that the ImageChecker might have detected, weren't detected.

I would like to point out that my experience has been that it is not size alone that determines whether a lesion will not be flagged.

The other thing I would like for your consideration is that if you look at data published previously by Dr. Sickles regarding the size of cancers detected in a screening population, that half of them are larger than a centimeter and half of them are smaller.

If you look at the 250,000 screened women or screened cases in the study submitted, you would assume that there should be no significant distribution difference in the size of cancers included in this very large population.

You would think that even with half the cancers being smaller than a centimeter, a very significant portion of those were flagged as well.

I would call your attention to the slides shown by Dr. Kass earlier, that those cancers were less than a centimeter by mammographic determination as well.

So, it is not size alone that determines whether a lesion will or will not. It is some specifically objectively analyzed features of the lesion.

DR. DESTOUET: Dr. Brown, what type of training did you go through prior to your utilization of the ImageChecker?

DR. BROWN: We had support from R2 that came out and sat with us, describing the equipment itself, and we used several test cases of larger cancers that I had pulled before we undertook the study.

DR. DESTOUET: So, part of your training was for the manufacturer to show you lesions that were not flagged by the ImageChecker?

DR. BROWN: As I said, we were one of the earlier sites and we were not part of the FDA trial of the data that you have.

Rather, we used it before the experience.

DR. DESTOUET: You were part of the preclinical trial, which is the part that I participated in.

DR. BROWN: That is exactly right.

DR. DESTOUET: I am still unclear as to what the training process is. Maybe either Dr. Stein or Dr. Kass could just explain to me, during the clinical phase, what the radiologist went through to learn.

DR. STEIN: In your documents there are three manuals that we use. There is the processor manual which is really for the technician's use.

There is the display manual, which we go over sections of the display manual with the physician, so they understand basically what button to hit.

Then the actual algorithm book, which we also go over with the physicians formally, in the course of a one to two-hour training session.

Then we identify the cases in the back as examples for them to, shall we say, study in depth of cases where we do make marks, on cases where we have missed.

Then they are actually shadowed by one of our applications specialists for a period of time, during that day when we load some cases on the alternator and just watch the physician use the device consistent with the labeling on the product.

You know, you hit the next case button on the Radex unit. The alternator moves forward to the next case. There will be no marks, of course, on the ImageChecker

displays.

They hit the button and if they have any questions about anything that happened, we answer them at that time.

DR. DESTOUET: Now, once this technology is disseminated, do you anticipate that you will have some type of training program for radiologists who utilize the device?

DR. STEIN: Our feeling is that the training that we did with the radiologists themselves in the course of this study, it is formalized. It is formalized on paper, in print, and with the test films that are included. These have actually served to be satisfactory.

Now, we do go back to the site, more from the technologist's point of view, to make sure if they have any questions about dropping the films in, and what might happen during the course of them loading the cases for the purposes of the radiologist's later review.

As Dr. Kass commented, and I think Dr. Cederbom would like to make a comment, too, training the doctors is the easiest part of all.

There is not much for you to do because you have to read off the films.

DR. DESTOUET: I actually tend to disagree. I think it is very easy to train your technologist how to digitize the images and hang up the images.

When you have, as you have in your examples, a

spiculated lesion that is not marked by the ImageChecker, training your radiologist to recognize that there are some lesions that are not going to be marked, I think is something that the company will have to consider.

There is a case here where there is a spiculated mass that is not marked, unless I am reading this incorrectly.

DR. STEIN: Again, this was the company's intention by example to do this. If we need to improve that aspect in our labeling and add more cases with further descriptions, of course we are completely amendable to do that.

DR. MALCOLM: I think the clarification that we are really trying to get at is, right now these radiologists were trained in this process that went through the study.

I think the big question is, with dissemination, if this product is approved, with dissemination, I think you are really getting at what kind of training will all these other physicians have.

That is, when the instrument is placed in the institution, will you go there, spend the days actually spent with the other radiologists. I think that is what you are getting it. I wasn't clear.

DR. STEIN: Yes, it is our intention. In fact, one of the amendments we provided specifically asked what type

of training. I thought we had elaborated that.

I think one better way to do it is I would like to invite Dr. Cederbom to give his comments. He was part of the investigation as opposed to the preclinical investigation and might give you better insight about his own experience and training of him and the staff at his facility.

DR. CEDERBOM: My name is Gunnar Cederbom. I am a mammographer, breast imager, at Oschner Clinic in New Orleans. I have no financial interest in the company. They have paid my expenses for coming here. I was a principal investigator during the prospective study.

The training we received, I think, was very, very adequate. We had the system available in our practice before we started to use it, for a full month before we started the study.

We studied the examples, and one thing was absolutely clear in my mind when I started using it. The way I read the mammogram, it makes no difference if the machine is here. I read the mammogram and interpret it as usual.

I flick on the ImageChecker just to see if there is any area that I might have overlooked. Whether a machine flags an area or not makes no difference in my final judgement of the case.

However, on many occasions it saved me from, when I was tired or when I was in a hurry or when I got a telephone call, to recheck an area where, sometimes to my surprise, I found even small lesions.

I want to emphasize that there was no difference between the sizes of the lesions that the machine picked up and that I picked up before I flicked on the device.

DR. SACKS: This is Bill Sacks from the FDA. I mentioned to you earlier that I had had a chance to look at this three weeks ago at the ACR conference.

Perhaps I am a good guinea pig in answer to your question. I went through about maybe 15 to 20 cases with Alan Stein sitting next to me.

It took me maybe 10 to 15 minutes and I felt perfectly comfortable just in that few cases, plus of course, three months of looking through the PMA prior to that.

This was really not going to be a problem for a radiologist's learning curve with the one useful piece of data that came out of my study of the PMA being that it is extremely important for every radiologist to know that this device misses lesions, and what kind they tend to miss, on the one hand.

On the other hand, it marks a lot of things that are just nothing that you need to look at. Those are the

things that save it, in most cases.

If you notice a lesion -- that four-by-two-by-two table that I showed -- where I had the dotted lines going one way or the other, the reason I dotted them is because the likelihood that you are going to change your mind about something that you have already seen and have already made a decision about whether you are going to work it up or not, just based on the fact that the ImageChecker either does mark something that you were not going to work up or does not mark something that you were going to work up is very minimal.

If you have decided this is nothing, you can even anticipate -- after a while you get into a game and you look at these and you say, that is nothing but I will bet you, when I press that white button, there is going to be a mark on that.

You have to sort of use it to get the feel for it and it was very, very useful for me to be completely comfortable with exactly the questions you are asking, to be able to sit there and actually use the device.

It really took minutes, combined with simply the information that this thing over-reads something fierce and misses, you know, asymmetries, skin thickening, nipple retraction and the like.

DR. ALAZRAKI: At this point I am going to turn

the meeting over to Dr. Romilly-Harper.

DR. ROMILLY-HARPER: Mr. Doyle will bring up the discussion questions and if we can have some participation from the panel?

We would like to discuss whether or not, as panel members, we believe that the PMA contains sufficient data to conclude that the M1000 ImageChecker can reduce observational errors by identifying overlooked areas on the original mammogram.

Any comments as to whether we don't think that we have sufficient data? Is it pretty much a consensus that we do?

DR. DESTOUET: I think the manufacturer has shown through its studies that it can, indeed, reduce observational errors made by the average radiologist.

DR. ROMILLY-HARPER: Thank you.

DR. GARRA: We agree on this side, too.

DR. ROMILLY-HARPER: Okay. You were quiet over there. If the device results in an increased sensitivity, is an increase in work-ups an important consideration.

I think this was discussed pretty extensively and discussed by Dr. Sacks. Any more comments on the issue?

DR. ALAZRAKI: Just one. I think clearly the discussions that we have had show that the device will increase the sensitivity from perhaps 80 -- if you accept 80

-- to 86, perhaps 88 percent. Certainly that is a very important consideration.

I just want to also -- not that I think it is terribly important, but the radiologist, as I understood the presentations, who participated in reading these studies as part of the R2 trial, all had at least probably double the number of experienced mammograph readings than are the minimum required by NQSA.

We are dealing with perhaps a more experienced mammography group of radiologists than may be encountered, once this is unleashed on the public radiology community.

The NQSA requires 480 mammographic readings per year and R2 required 1,200 readings per year of any radiologist participating in the study.

DR. STEIN: The main reason for this, again, is only because we didn't want the study to extend on and on, and we wanted to achieve statistics in a reasonable period of time.

There was no other magic resume. We assume and presume that if a radiologist is NQSA certified, they are qualified.

DR. ROMILLY-HARPER: I would even make a comment that 1,200 a year is a pretty basic number for most radiologists, even at a training level. Most radiologists who are reading mammograms, at any point in time, do about

1,200 a year.

DR. ALAZRAKI: Also, what that means to me is that the less experienced, perhaps, radiologists using this device will benefit more from the increased sensitivity.

Now, there may also be a fall in specificity for that group which certainly will exceed the specificity fall, since you showed non-significant in the group of radiologists who participated in the study.

DR. GARRA: Clearly, the evidence shows that if there is an increase in work ups, which we didn't see but we expect, it is not going to be a major problem which is, I think, what the concern of the FDA was, and I think that has been adequately addressed.

DR. ROMILLY-HARPER: Yes. So, is there consensus that we can move on to question number three?

If you conclude that the M1000 ImageChecker helps to minimize observational errors by identifying overlooked areas on the original mammogram, let's discuss whether or not we believe the PMA contains sufficient data to conclude that this can be done without unnecessarily increasing the number of patient work-ups significantly.

Some of the information that Dr. Sacks specifically provided for us, I think, helps us with this question. Any other comments?

DR. DESTOUET: I think this is unfortunately a

question to which we don't have an answer. The problem that we face now with mammography is the lack of specificity.

That was addressed in the New England Journal paper. We all know that mammography is sensitive, but that we find things that don't turn out to be cancer, either with biopsy as the gold standard.

As Dr. Sacks has pointed out, one of the barriers that we really need to overcome is how do we increase our sensitivity. How can we find cancers that we are not finding now.

Ultimately down the road, we are going to have to work on specificity. That comes, in many cases, just with training, just with following those lesions that you send to biopsy that turn out not to be cancer, looking at the lesion characteristics, and hoping that in the future you don't send those women to biopsy any more.

We also now have tools at our disposal, with image guided biopsies, where we can offer women a less invasive way to biopsy lesions.

I think that even though this device may certainly not increase our specificity, even if it decreases our specificity a little bit, we can handle that, by hopefully increasing the sensitivity enough that we are saving more lives in the future.

DR. ALAZRAKI: I have another, perhaps it is a

question in the data that R2 collected. How about women with dense breasts, young women with dense breasts?

They are part of the screening population and a very important part because mammography traditionally fails often in women with dense breasts. It is not as sensitive as it is in women with fatty breasts.

Of your large sampling that you have, can you identify women with dense breasts and how the computer-aided device did?

DR. STEIN: We have, as you would expect in this series of cancer cases, a normal age distribution. We cannot differentiate any difference in sensitivity of the device as a function of age. Density, we don't exactly even know how to formally define. It does range.

DR. ALAZRAKI: But there was no difference as a function of age.

DR. STEIN: No, not at all. Particularly if you look at the calcification code, we hit 396 out of 404. We hit it all.

DR. ROMILLY-HARPER: I think it is because the image was digitized also. At that point in time you diffuse any variation depending on density, any variability.

DR. ALAZRAKI: You mean if the dense breast is uniformly dense.

DR. ROMILLY-HARPER: Yes, and the characters that

the ImageChecker detects would be the same, whether the breast is dense or whether it is fatty.

Any other comments? We will go on to question number four.

Let's discuss whether the labeling of this device, including the indications for use, is appropriate, given the data provided in the PMA, or should it be revised or amended with respect to the following:

Claimed ability to flag overlooked cancer; relative ability to detect masses and calcifications; or any other characteristics or claims of the device.

I would like to give this a little time and thought because I think this is important. Any comments?

DR. GARRA: I have a comment and a question. Regarding some of the, I guess it was advertising literature that was reproduced in the application, there are some claims for how many extra cancers are going to be found and things like that.

Since you are going to have -- and this also gets back to Dr. Sack's discussion -- the same person who is initially reviewing the mammogram is going to be looking at it again after being flagged, it makes me wonder if the improvement is going to be somewhat less than you predicted; something less than 30 percent perhaps.

The other thing was the population distribution of

the cases where you had priors. It may not be a match for the population of normal screening patients, since you selected these patients based on positive screens rather than all screens.

For instance, you have this population of patients where you had prior mammograms. There are quite a large number of patients where the panel was five for five saying that there were 38 patients where five said there was something suspicious on the prior.

That may be a function of the fact that you had the time frame at which the previous mammogram was acquired versus the current mammogram, because they were all diagnosed as having cancer on the current mammogram.

The prior one, if it was acquired close to the recent one in time, would tend to be more positive. I don't know what the distribution would be but I suspect it is a little bit skewed in some fashion.

DR. STEIN: We have those data. The median was about 14 months. They normally distributed around there. Of course, it is a little shorter on the nine month side than the 24 month side, but it is fairly normal distribution around that.

These are patients who, if you wanted to say on average, would have had their cancers detected, or could have had their cancers detected 14 months sooner.

DR. GARRA: I guess the main question I had was, in looking at the manual for the viewer station, there was no indication to the radiologist reviewing the study that they should disregard a negative marker on the mammochecker versus saying, oh, I thought there was something there but the mammochecker says no, so maybe I can blow it off.

Your instructions are very general about that and I think that is a concern that all the panel members have, that they need to be more specific, the instructions that you need to give to the radiologist.

DR. STEIN: In the sense, Dr. Garra, that the corollary would be, if the ImageChecker puts a mark on the area, it is up to you, doctor, to identify whether you act on it or dismiss it.

If you don't see a lesion, you should also do the same thing. If you don't see a mark and you see something --

DR. GARRA: You should not change your judgement based on that. That was the key thing that was sort of missing in those instructions.

DR. STEIN: That was not an intention.

DR. GARRA: The instructions were, I thought, pretty reasonable. They didn't bias a radiologist one way or the other.

I think over a period of time what would happen is the person would get biased, especially if they had a couple

of experiences where the mammochecker found a couple of subtle lesions that they had missed.

They would tend to rely more and more on the mammochecker unless you gave those specific instructions to the contrary.

DR. STEIN: I do agree with you except to the extent that it is a perceptual aid, since it is never in the interpretation, it is only telling you that you should look more carefully.

DR. GARRA: It doesn't say that in the instructions, though.

DR. STEIN: It is only ever described in the instructions as an aid to the radiologist. It is a perceptual aid, not an interpretive aid.

DR. ROMILLY-HARPER: I think we are all trying to say that we need to go beyond that because we need to also reinforce to the radiologist that if something is not visualized by the mammochecker, that they should not disregard their initial observation.

DR. STEIN: We would certainly be happy to modify the labeling to that extent.

DR. GARRA: I believe you did that in your on-site training. One concern would be that when the unit is purchased, you provide on-site training.

In a lot of departments the people sort of come

and go. They might have two or three staff changes within a year.

They might not even notify you, necessarily, that Joe blow is now reading the mammograms versus somebody else. There has to be some mechanism to assure that these new people, who know how to read mammograms but don't know how to use the mammochecker, can be informed of that.

DR. STEIN: We would look for some advice from FDA on that labeling.

DR. ALAZRAKI: I still want to come back to the issue of the dense breasts. In association with this claimed ability to flagged overlooked cancers, I am not convinced that even if the density of the breast is uniform that you still aren't facing -- and I think you are -- a decreased sensitivity to detect lesions, because your noise level has to be much higher.

To pick out a small cancer has got to be diminished, even with a digitized image, it seems to me. So, I haven't seen the data here specifically looking at the women with dense breasts, to show that it is as good as it is in all other breasts, and that the same cautions that apply in interpreting conventional mammograms when there are dense breasts should still probably apply here, unless there are specific data to the contrary.

DR. SEGERSON: I would like to take a chance to

answer that question, and I would like to preface it by saying that I do not practice mammography. Perhaps it sounds somewhat strange.

Let me just try to re-emphasize what the ImageChecker is programmed to do. It is really programmed to flag or mark areas that are on the mammogram, that are visible.

The problem of finding cancers in dense breasts, to my understanding, is very difficult because of the inherent problem of the breast parenchyma being dense in younger women.

If it is not on the film, the ImageChecker is not going to find it. If it is not there, it is not going to find it.

This is not a device to enhance what the radiologist can see. It is a device to make sure that the radiologist has the opportunity to find something that is, in fact, visible. If it is not there, it is not going to flag it.

DR. ALAZRAKI: That is exactly what I am saying, I think.

DR. SEGERSON: I agree that we should put something in our training manual to indicate that if you, the radiologist, find something -- not the ImageChecker, not your colleagues -- nobody should dissuade you from following

that lesion. I think we practice that way all the time and the ImageChecker should be viewed the same way.

DR. ALAZRAKI: Perhaps we might even consider in the labeling just saying simply that conditions of the breast which diminish the sensitivity are not altered by the use of the ImageChecker.

DR. SEGERSON: Once again, it is a device to help the radiologist see what is see-able, not to pick up invisible lesions.

DR. ROMILLY-HARPER: Thank you. Any other comments?

DR. SMATHERS: I think I would like to see the labeling characterize the strengths and weaknesses of the device a little further.

As I gleaned from the reading and the presentations, it picks up microcalcifications far easier. I think you ought to take credit for that and tell the radiologist that they will probably find that it detects the great majority of microcalcifications, in that most of them will be within two-and-a-half millimeters of each other.

That is the way it is programmed. I mean, this is the way it works. Understand its strengths and its weaknesses.

By the same token, I think you ought to then also tell them that minor tissue differences, it is not as

strong. A percentage of those, it should find, are going to be lower. It is 60, 70 percent down there. It is not going to be 95 percent.

I think this type of information, while phrased far more elegantly, has to be in the instructions to the physician, so that they know the strengths and the weaknesses of the device they are using and properly interpret what it is telling them.

DR. ROMILLY-HARPER: Thank you. Any other comments? I think just to reiterate, I think two very excellent points that were made that I would like to see you think strongly about and work with the group, the FDA, in designing appropriately labeling for physicians.

Number five. Are there any issues not fully addressed in the PMA? If so, should these be resolved before the PMA is approved? Can these be addressed by postmarket surveillance or postmarket study? Any comments?

DR. ALAZRAKI: I think I am satisfied with the way we have resolved the dense breast issue. I also want to point out that I think we are well aware of the fact that the study groups that have been presented to us are individuals being screened who have had, as I understand it, no prior interventions into the breast. They are not post-operative except for a very small, 60-some-odd, who had had breast surgery.

They are not breast implant patients or other interventions into the breast. So, the data that we have concern a screening population of uncomplicated breasts.

DR. STEIN: First of all, the sensitivity numbers, which were identified in the precision study III-A, were from 1,083 women out of a very large screening pool.

Those included women who might have had prior surgery. It was those women who had cancer at that time.

The women we excluded, to give an indication of the opportunity to improve screening detection, was by looking at those priors.

The sensitivity claims that are based on study III-A, are based on an unselected consecutive 1,083 case series.

DR. ROMILLY-HARPER: Many of them or all of them had had surgery?

DR. STEIN: Probably actually very few of them had surgery, because this was their first incidence of cancer. They may have had suspicious biopsies or so on.

DR. DESTOUET: I think with proper labeling, that there remain no other significant issues to be addressed. We certainly don't need a postmarket surveillance and study that I can see.

DR. ROMILLY-HARPER: I would just encourage R2 Technology, with the interesting information we have gotten

from the numbers that you studied, if you could continue at least having some type of not necessarily mandated postmarket surveillance, but some type of surveillance so that we can evaluate the different types of breasts, and probably get more information about the true utilization and benefits of this instrumentation, that would be very helpful for us as users particularly.

Any other comments or questions? Do we have number six?

MR. DOYLE: No.

DR. ROMILLY-HARPER: Okay, that is it.

DR. ALAZRAKI: Okay, we will now move to the panel's recommendations concerning PMA P-970058, together with the reasons for the recommendation, as required by Section 15-C-2 of the act.

The panel is being asked to make a recommendation concerning whether this PMA should be found approvable, approvable with conditions, or not approvable.

A recommendation must be supported by data in the application, or by publicly available information.

The recommendation may take one of three forms. One, the panel may recommend that the PMA be approved with no conditions attached to the approval.

Two, the panel can recommend that the PMA be found approvable subject to specified conditions such as

resolution of clearly identified deficiencies cited by the panel or by FDA staff.

Examples can include resolution of questions concerning some of the data or changes in the draft labeling.

The panel can conclude that post-approval requirements should be imposed as a condition of approval. These conditions may include a continuing evaluation of the device and submission of periodic reports.

If the panel believes such requirements are necessary, the recommendation must address the following points:

A, the reason or purpose of the requirements; B, the number of patients being evaluated; and C, the reports required to be submitted.

The panel may find the application not approvable.

The act, section 515-B-2-A through E states that a PMA can be denied approval for any of five reasons.

Briefly, three of these reasons that are applicable to our deliberations and decisions are, one, there is lack of showing of reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the labeling.

To clarify the definition of safe, there is a reasonable assurance that a device is safe when it can be

determined, based on valid scientific evidence, that the probable benefits to health, from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against safe use, outweigh the probable risks.

The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

Two. The PMA may be denied approval if there is a lack of showing of reasonable assurance that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling.

The definition of effectiveness is there is a reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target population the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use, and warnings against unsafe use, will provide clinically significant results.

Three, the PMA may be denied approval if, based on a fair evaluation of all the material facts, the proposed labeling is false of misleading.

If the panel makes a non-approvable recommendation for any of these stated reasons, it is stated that we identify the measures that we believe are necessary, or steps which should be undertaken, to place the application in an approvable form. This may include further research.

The underlying data supporting a recommendation consists of information and data set forth in the application itself, the written summaries prepared by the FDA staff, the presentations made to the panel, and the discussions held in the panel meeting, as set forth in the transcript.

I am being reminded that before we vote, we will move to the second half-hour open public hearing session.

Agenda Item: Public Comment.

DR. ALAZRAKI: You are reminded that the same identification processes and disclosure requirements announced for the first open public hearing session apply to this session as well.

If there are any individuals wishing to address the panel, please raise your hands and identify yourselves now.

Does R2 want to make any additional remarks to the panel?

DR. STEIN: No, thank you.

Agenda Item: Panel Recommendations and Vote.

DR. ALAZRAKI: Now we need a recommendation from the panel for consideration.

DR. DESTOUET: Madam Chairman, I move that the PMA be approved without condition. The indication for use, ImageChecker M1000 system for computer-aided detection with image analysis and visual display capabilities is intended for use as an aid for radiologists routine screening mammograms.

DR. ROMILLY-HARPER: Second.

DR. ALAZRAKI: Okay, thank you. We now have a motion on the table for approval without conditions. Any discussion?

DR. MALCOLM: I just want to make sure. I am assuming this is correct, that the FDA will work to improve the comments that we made with regard to labeling of the equipment.

MR. DOYLE: That is part of our requirement to complete the labeling review.

DR. GARRA: I have the same question, because in our little orientation that we got this morning, it said that without condition meant that the labeling as it was in here would stand. I don't think the panel wants that.

DR. ALAZRAKI: A question, Mr. Doyle. Do we need to state that type of condition here?

MR. DOYLE: I think you do, yes.

DR. ALAZRAKI: Is that implicit in the discussion?

MR. DOYLE: You have to put that in.

DR. ALAZRAKI: Okay, then we need an amendment to the motion, if you so wish.

DR. DESTOUET: I move that the PMA be approved with the condition that the manufacturer works with the FDA to improve labeling considerations as so stated by the panel.

DR. ALAZRAKI: According to rules, you have to withdraw your previous motion and the person who seconded it has to agree, and then we have to have a new motion.

DR. DESTOUET: Madam chairman, I withdraw my previous motion for approval without conditions.

DR. ROMILLY-HARPER: Agree.

DR. ALAZRAKI: Now, new motion.

DR. DESTOUET: I move that the PMA be approved with condition that R2 Manufacturing Company works with the FDA to put in the labeling the advice of the panel.

The indications for use, the ImageChecker M1000 system for computer aided detection, with image analysis and visual display capabilities is intended for use as an aid for a radiologist reading routine screening mammograms.

DR. ROMILLY-HARPER: Second.

DR. ALAZRAKI: Thank you. Any further discussion of the new motion, seconded, on the table?

If there is no discussion, then we are ready to vote. All in favor of the motion, raise your hands.

[Six hands raised in favor.]

DR. ALAZRAKI: Six in favor. That includes all of the voting members who are present, so it is in essence a unanimous approval.

Is there any other business that we need to conclude? Oh, yes. The FDA would like all of the panel members who voted to give a very short, concise summary of the reasons that they voted as they did. If we could start with Dr. Garra?

DR. GARRA: I voted to approve the device with the condition that the labeling be altered to caution the radiologist against changing their diagnosis based on a negative result from the mammochecker, which is I believe what the manufacturer also intended.

The evidence is pretty convincing that the device can identify lesions that could be missed by a human observer, and should be of a great benefit.

DR. ALAZRAKI: Thank you. Dr. Smathers?

DR. SMATHERS: I would concur. I think the only hazard is that a radiologist might change their view of a lesion, or even less of a chance, might someday use this as the crutch instead of their own mind. So long as those two things don't happen, it is going to be a great benefit.

DR. ALAZRAKI: Thank you. Dr. Griem?

DR. GRIEM: Considering the doubling time of some tumors that are 100 days and that a miss that is then followed up a year later essentially has metastases, and considering that the machine has no real risk from the design and shock hazard and so forth, and the benefit of this PMA and the computer-aided diagnosis, particularly of a tired radiologist who is bothered by phone calls and other things, and that this really provides sort of a mechanical second reading which then, in such sense, seems to function flawlessly, I think it will be a real help to the evaluation of the mammogram.

If Dr. Sacks' evaluation of it suggests that we might save about 11,000 lives, I think there is a real cost/benefit ratio here. That is why I voted for it.

DR. MALCOLM: I also approve of this device. I think there are two key points and I think that Dr. Griem just mentioned them, and that is saving cost, and morbidity for the patient, and saving lives, which I think is the most important thing, and that is why we are here in medicine.

I think this device will help and assist the mammographer in doing so. I think that the company, at least looking at the data, has provided all the necessary study criteria to demonstrate to us that this device will do this and, therefore, I approve it.

DR. ALAZRAKI: Thank you. Dr. Destouet?

DR. DESTOUET: I think the manufacturer has shown that this is a safe and effective device, and there is no question that mammographers need all the help they can get.

So, time will tell whether the specificity is lowered to such an extent that we need to re-look at this piece of equipment. I think as it stands now, it should be a benefit.

DR. ALAZRAKI: Thank you. Dr. Romilly-Harper?

DR. ROMILLY-HARPER: I concur with my colleagues. As a practicing radiologist, I think this will be a significant tool, not only for the experienced radiologists, but for the young radiologists, the newer ones on the block, to improve their ability to diagnose breast cancers.

DR. ALAZRAKI: Thank you. Patricia Whalen is the consumer advocate on the panel. Although she is not a voting member, we would like to hear also what you think.

MS. WHALEN: I am delighted with the panel's approval of the application. I think for the 36,000 women who are missed and get false negatives, this is a great boon. I also agree with the labeling considerations that were raised.

DR. ALAZRAKI: Thank you. Mr. Doyle?

MR. DOYLE: I would like to once again remind everyone here that the remaining meetings of this panel this

year will be on August 17 and 18. We anticipate a heavy schedule and are scheduling two days for that meeting.

Then another meeting in November, on the 16th, one day at this time.

Finally, before I turn it back to Dr. Alazraki for closing, I would like to remind the panel members that they are required to return all the materials they were sent pertaining to this PMA.

Materials you have with you may be left at your table and any others should be sent back to me here at the FDA, as soon as it is convenient.

DR. ALAZRAKI: Thank you, Mr. Doyle. I want to thank our lead reviewers, Dr. Destouet and Dr. Romilly-Harper, who put in a lot of extra time and work and energy to help us analyze the data that we had before us, and reviewing all of the sponsor's material, and for the recommendations to the FDA for the M1000 ImageChecker.

I think the panel did a great job. Everybody knew the stuff and I look forward to our next meeting in August.

Since there is no further business -- sorry, Dr. Yin?

DR. YIN: I would like to take this opportunity to welcome Dr. Alazraki as our chairman from here on in; is that correct?

DR. ALAZRAKI: Not indefinitely.

DR. YIN: At least for the next four years. So, we are very, very pleased. Thank you for coming aboard. I think I should also introduce Bob Doyle. This is your first meeting as executive secretary. I also want to take this opportunity to thank Jack Monahan. He was our former executive secretary. So, thank you, Jack, and we welcome the new one.

Today, I do want to thank all of you for doing such a good job; precise and up to the point and I would like to thank the sponsor for doing a good study. So, all in all, thank you all. Have a nice trip home.

DR. ALAZRAKI: With that, we adjourn the meeting.

[Whereupon, at 1:55 p.m., the meeting was adjourned.]